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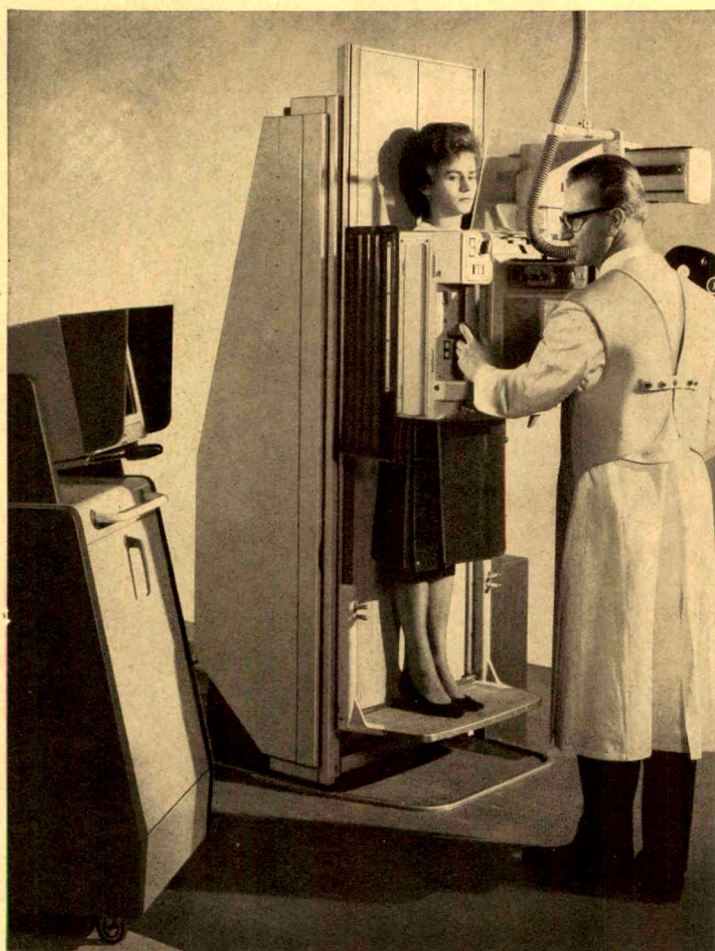
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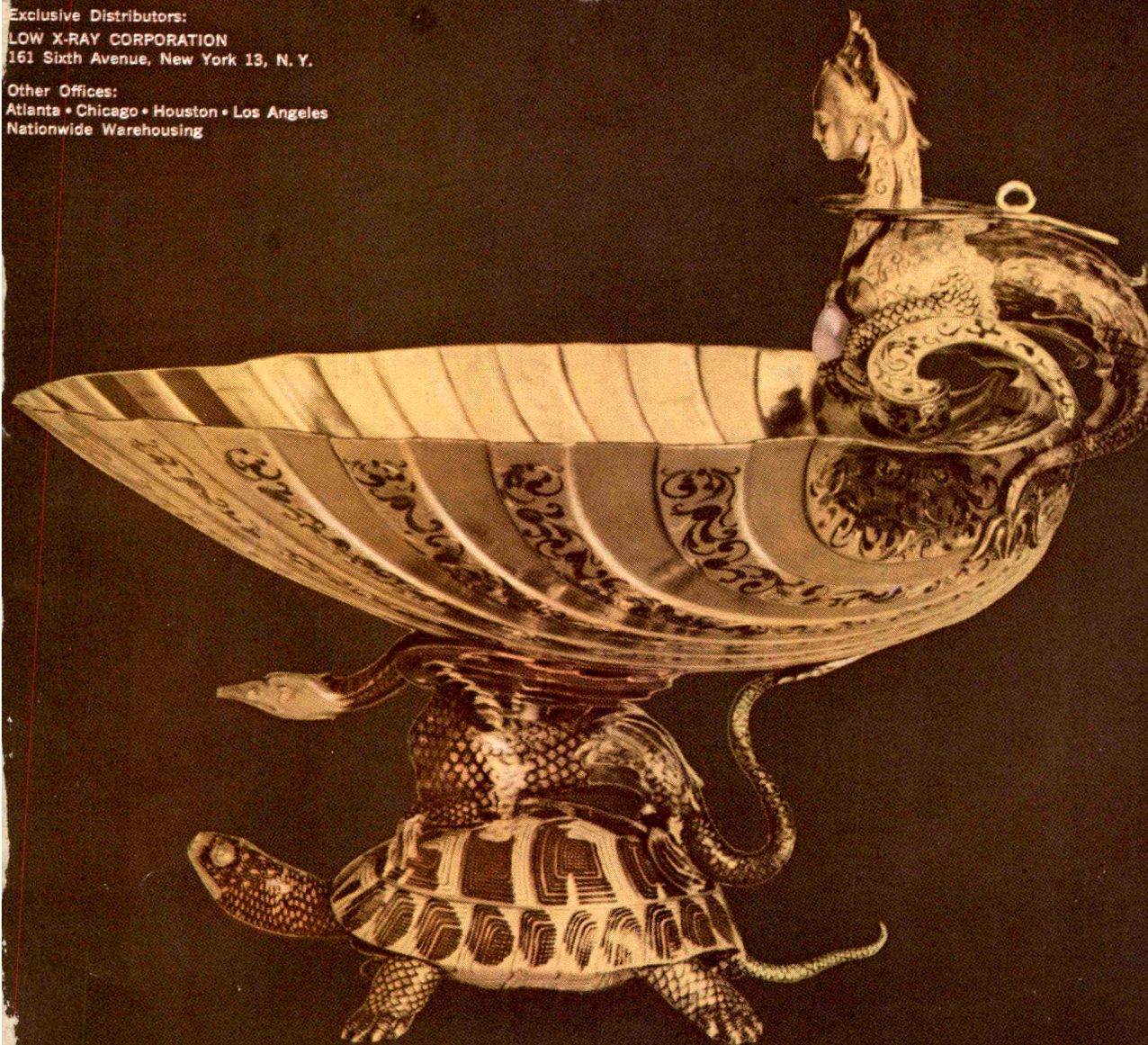
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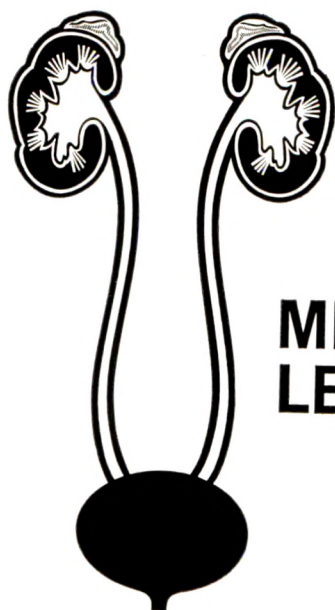
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*Margulis, A. R., and Heinbecker, P.: Am. J. Roentgenol. 86:103 (July) 1961.

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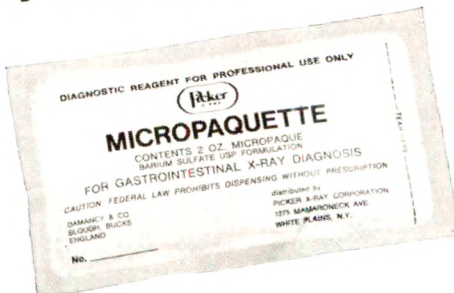
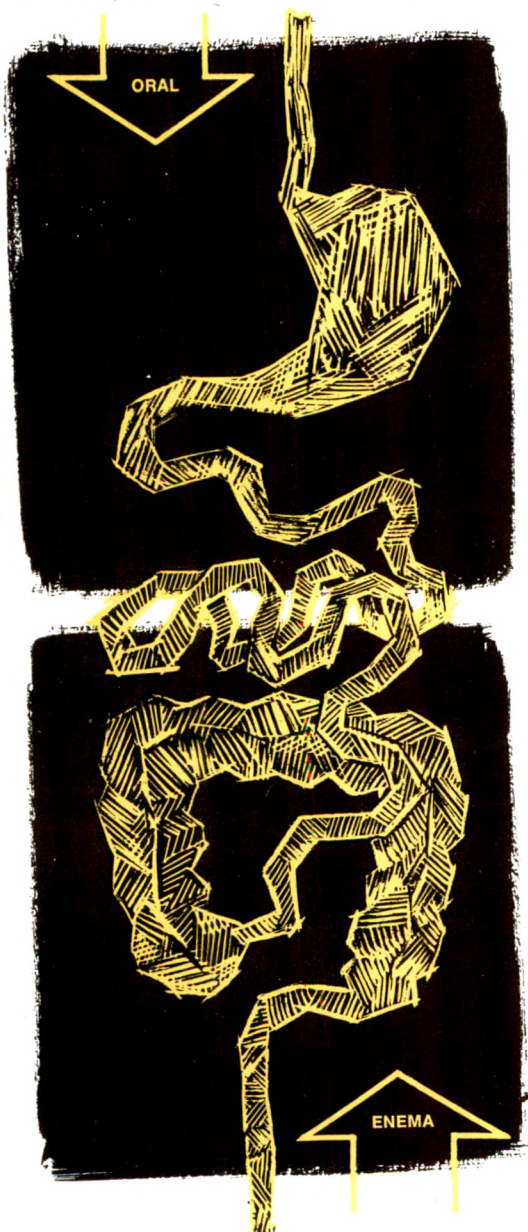


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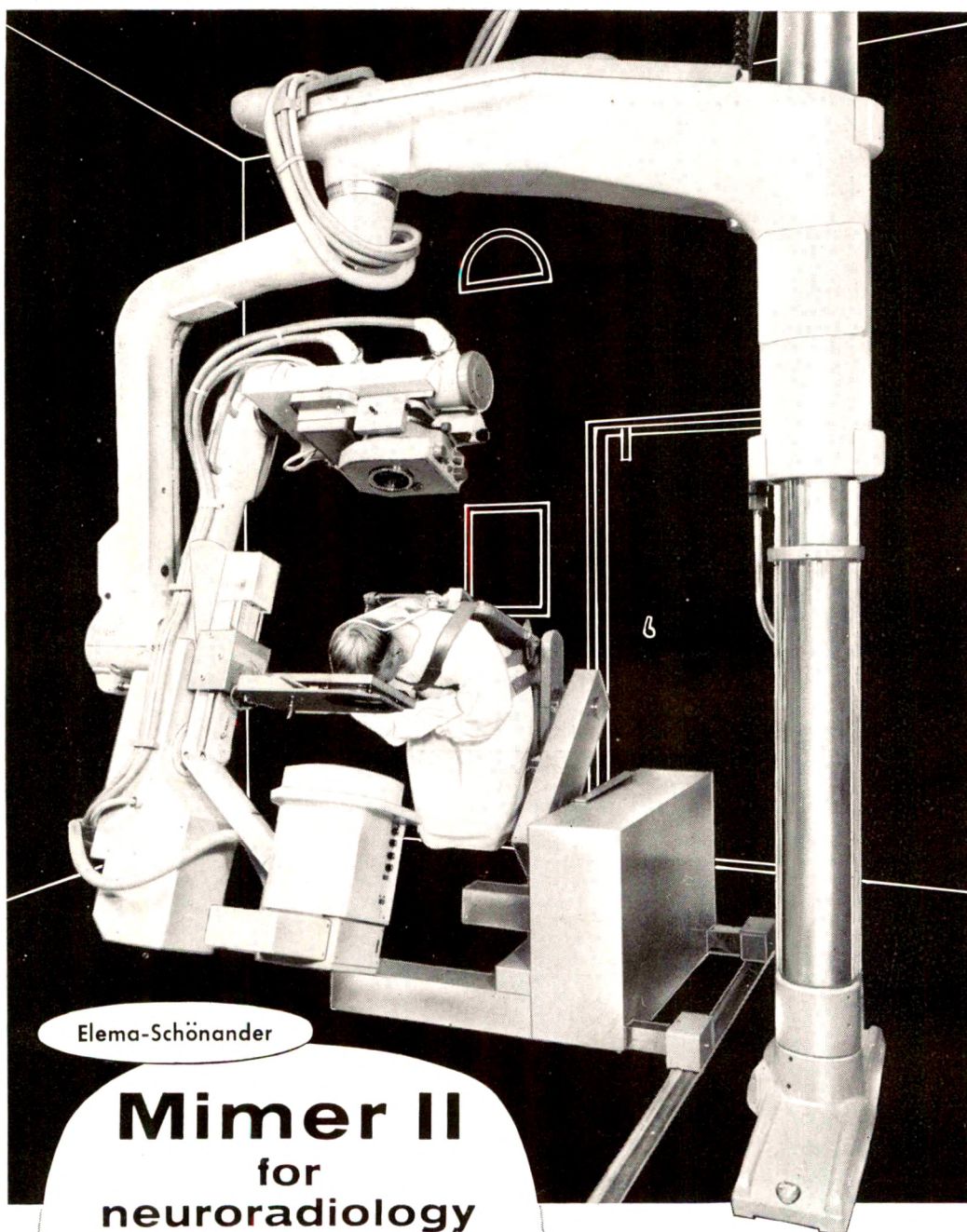


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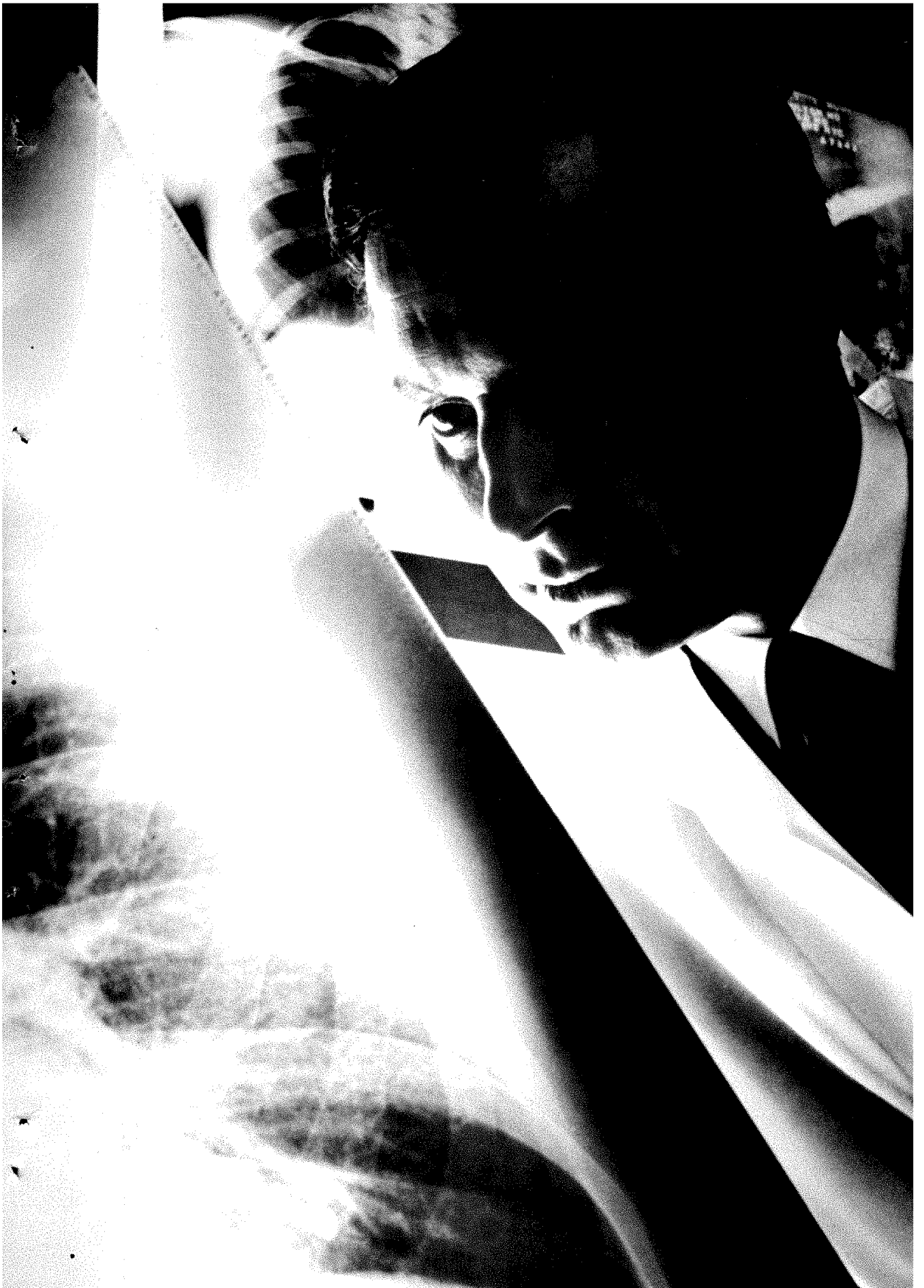
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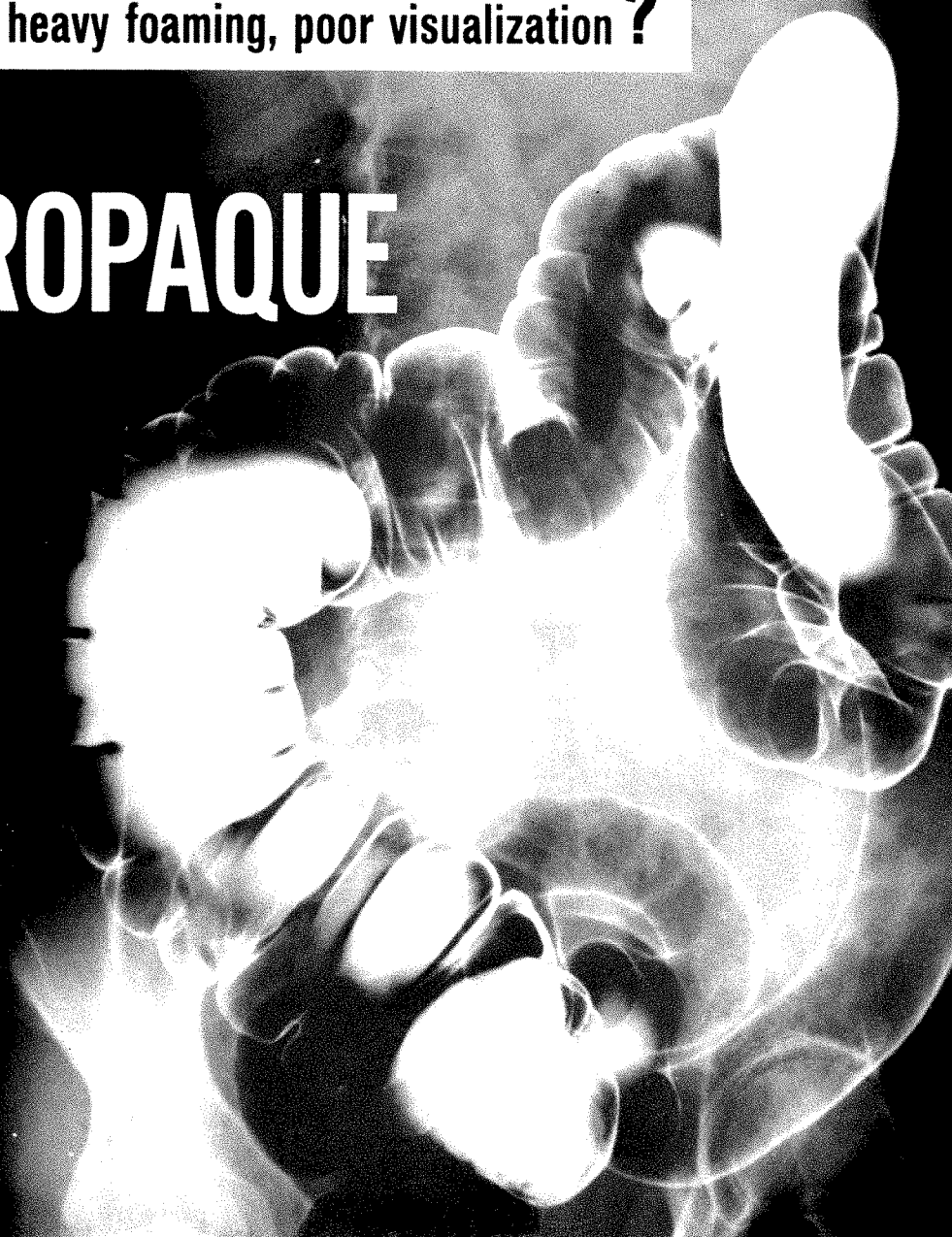
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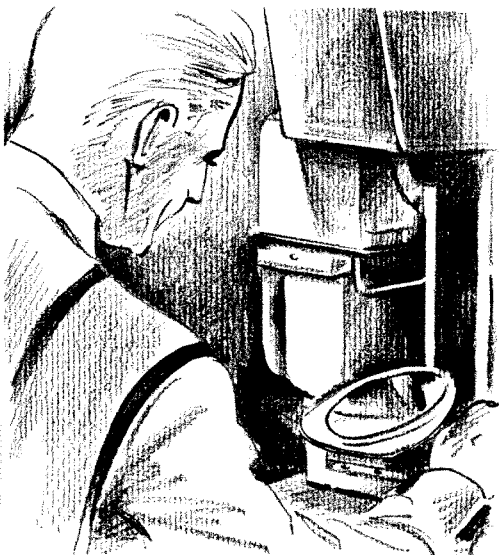
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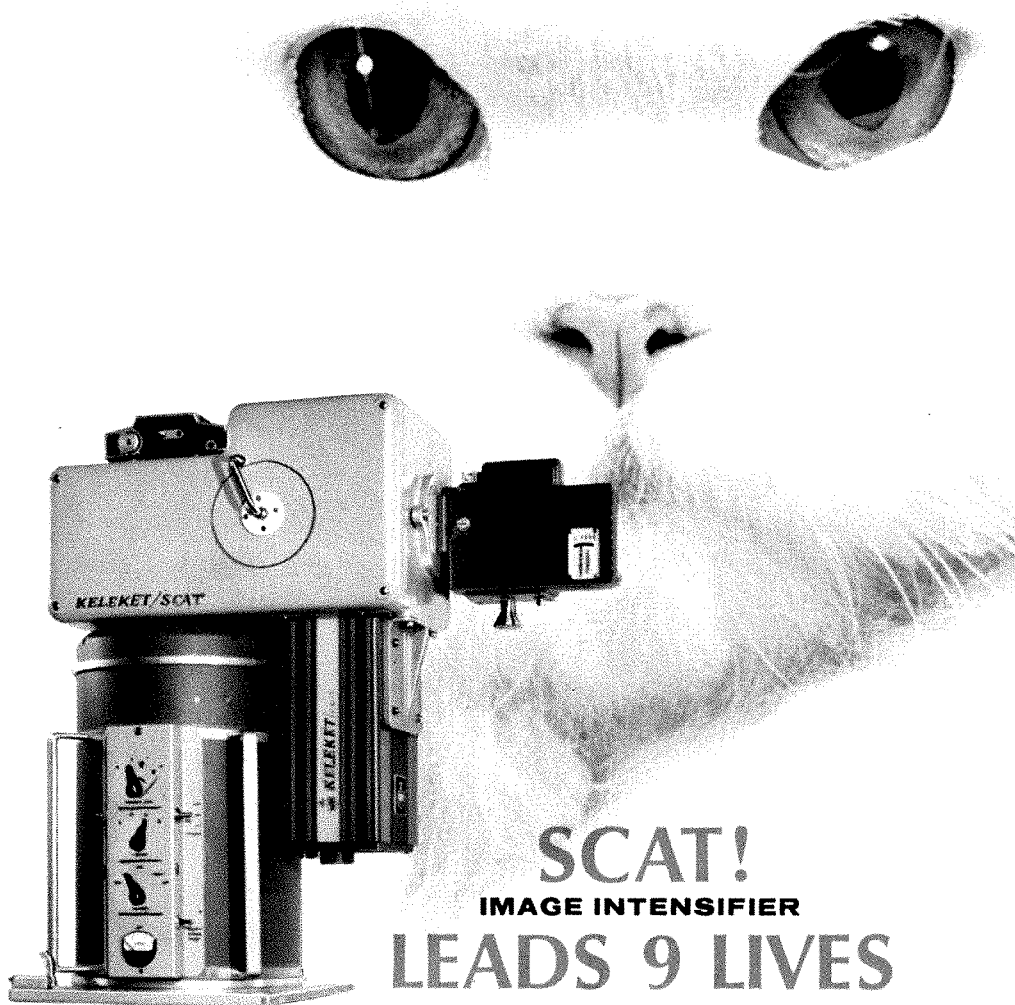


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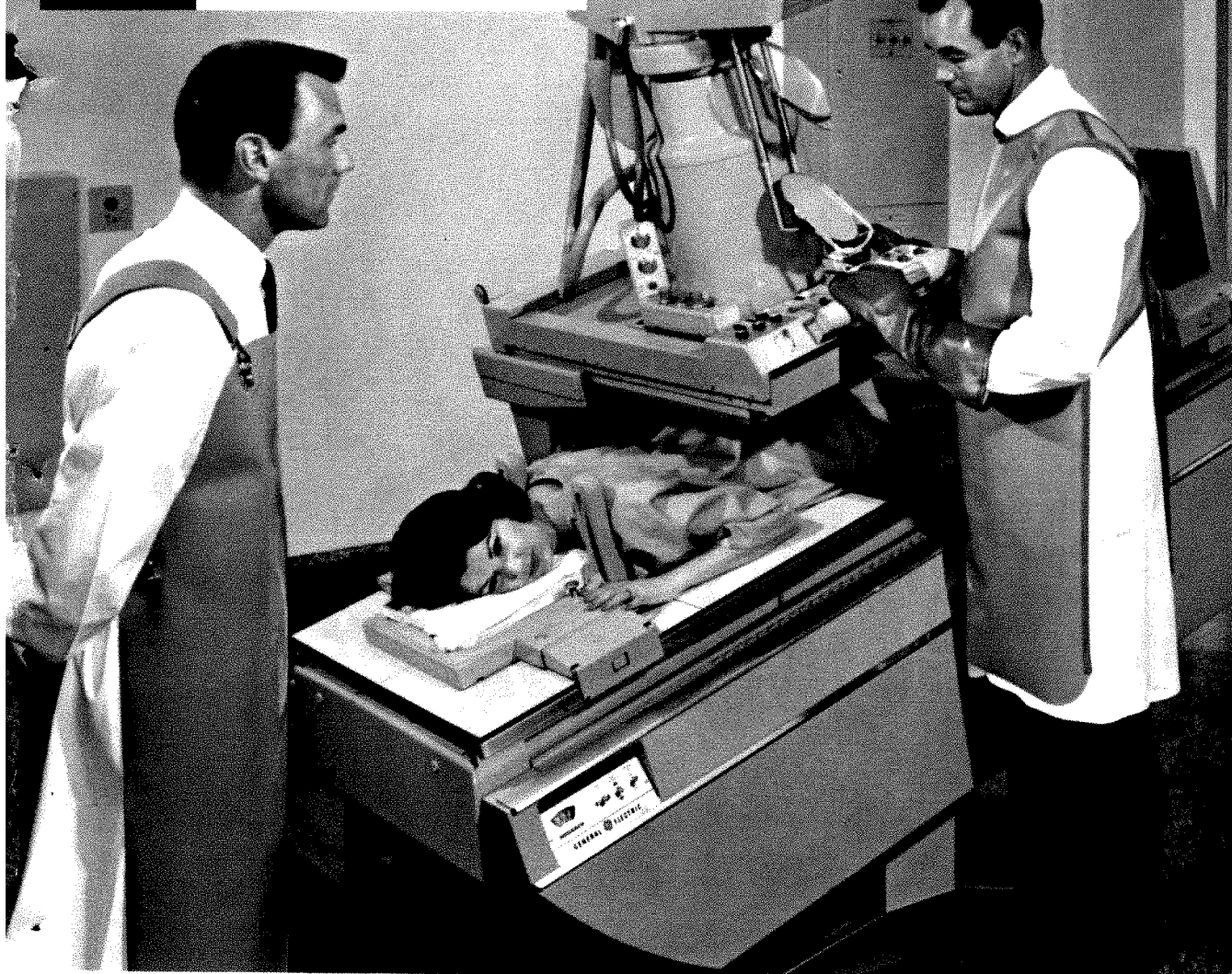
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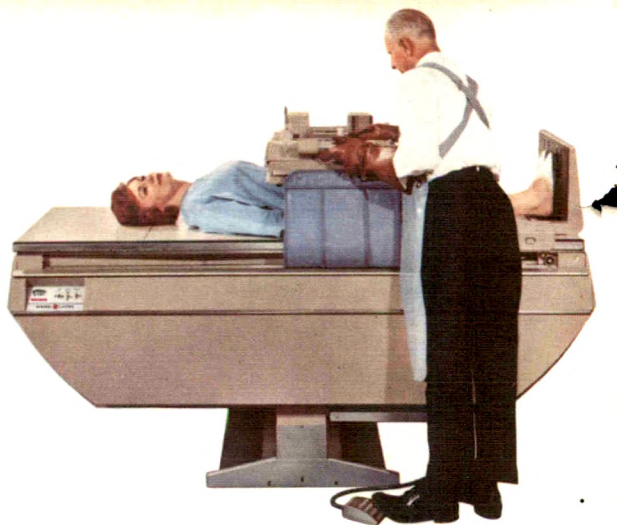
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With patients subject to fainting or vertigo, prevent interruption of examination and danger of injury with secure safety harness. Quickly adjustable harness will support 300 pounds.

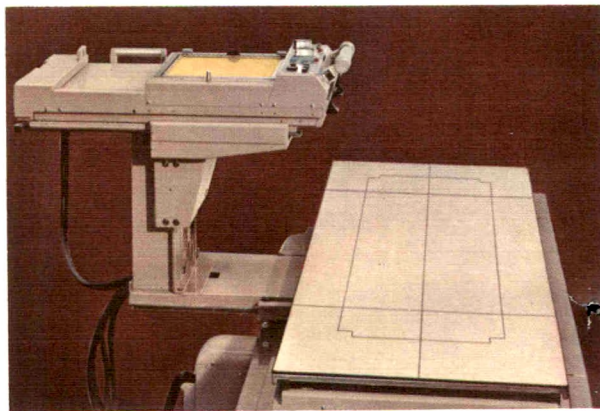


Grasp Handles

Give the patient a secure feeling and eliminate extra personnel to hold the patient in angulated position. Handles are easily attached or removed at any point on table side. Positive locking device for safety.

Convenient Front-Loading Spot-Film Device

Here's the perfect example of how procedural observation and consultation by General Electric engineers results in product innovation. You are able to quickly load the square cassette (12" x 9 1/2") into the front of the Model 63 spot-film device without worrying about proper cassette positioning. Carriage mechanism is simplified, eliminating gears, belts and pulleys that interfere with spot-film work. And glide-back parking permits table top to be completely cleared during radiographic procedures or for patient care. The square cassette, front loaded; Model 63 spot-film device is "common-sense" equipment that YOU asked for. We took it from there.

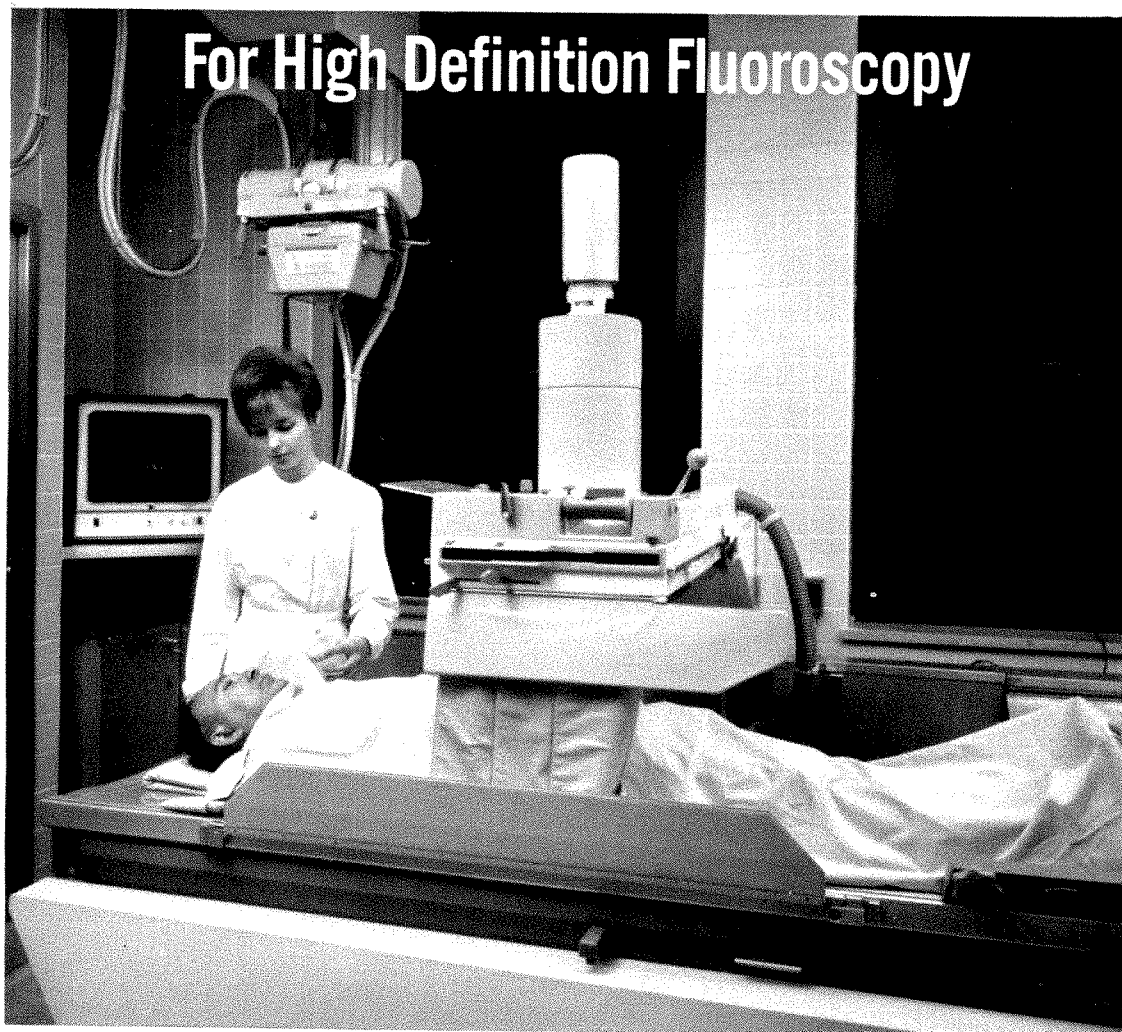


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NORELCO PLUMBICON TV

For High Definition Fluoroscopy



Every unit in the Plumbicon Television Chain is a Norelco component — manufactured to offer you a completely matched and integrated TV fluoroscopy system. The Plumbicon Chain, in combination with a Norelco, 6", 9", or 9 7/8" Image Intensifier is unequalled for convenience and reliable, versatile performance.

Features include:

- Good camera sensitivity at relatively low radiation levels
- No blurring or image lag
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- Enhanced stability and ease of servicing
- Can be used with any video recorder
- Possible to connect several chains to one sync generator
- Compatible with all standard closed circuit TV

PICTURE THE BEST with PLUMBICON TV



NORTH AMERICAN PHILIPS COMPANY, INC.
Professional Products Division, 100 East 42nd St., New York, N.Y. 10017

H-46

xxiii



The real story is on the inside of the Ultima X-Ray Control Unit

The story is modular unit construction. That's what makes the Ultima X-Ray Control Unit unique. It means you can build it to your exact requirements without the cost or waiting normally associated with custom construction. You can actually choose from 1056 different possible combinations of controls, timer modes, and special features. You can also choose from either 400 or 500 MA models with solid state or thermionic valve or voltage rectified transformers.

After you make your selection, Standard will quickly assemble an Ultima from pre-fabricated, pre-tested modular component units ready in stock. Result? The control unit to fit your exact requirements in the fastest possible time.

You get more than just choice with the Ultima X-Ray Control Unit. You get flexibility too. At any time, simply changing modules, you can modify or up-grade the Ultima to meet new requirements. For example, if you wish to convert from the control of conventional 60-cycle x-ray tubes to control of high-speed 180-cycle

x-ray tubes, the Ultima can be modified quickly, on-the-spot, and with minimum cost.

Servicing is simplified too. Modules and components can be serviced or replaced individually as required without dismantling the entire unit. Careful design has kept all parts readily accessible and easy to reach.

Most important, you benefit from Standard's 53 years of experience in producing durable, dependable, and quality x-ray equipment. Every bit of this experience has gone into the design and production of the Ultima X-Ray Control Unit.

Your Standard X-Ray dealer will be happy to explain the wide choice of options and other features available to you. He can also tell you about Standard's other superior quality x-ray equipment. For the name of your local dealer and a copy of our new catalog, just contact us.

STANDARD

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a subsidiary of Cenco Instruments Corp.
1932 N. Burling St., Chicago, Ill. 60614

STX-6/011

GRAPH-O-MAT 90



a chemistry for all times

The choice is yours — where an x-ray department requires extra speed but is unwilling to sacrifice quality, the new **Hunt Double Capacity System** is the answer. Where access time is considered a more important factor, the 90 second dry-to-dry processing cycle will be your decision. The **Double Capacity System** — engineered and developed by Hunt offers:

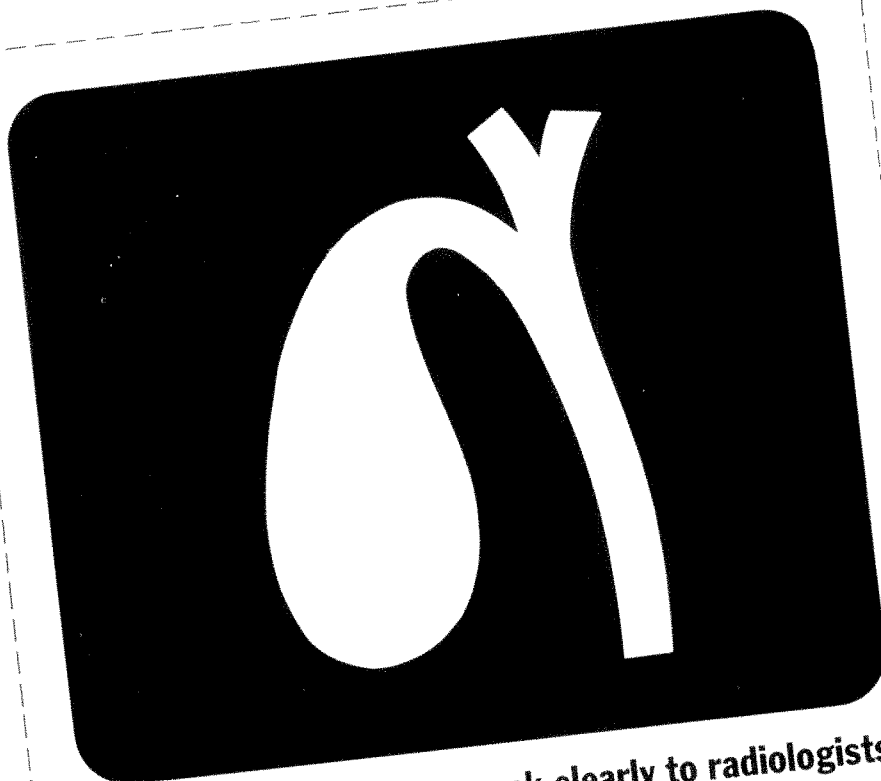
- fast access time, (double conventional film capacity)
- films of diagnostic quality comparable to the best quality of the 7 minute cycle
- and the choice of using any brand of film; X-ray departments using a particular film emulsion can maintain the high standards established through long association with a favored film.

■ Whatever decision you make — think of **Hunt**. Our chemistry, Graph O-Mat® 90 is compatible with both processing cycles and all brands of film. Our sales force will offer you knowledgeable advice on every aspect of the new ultra-fast processing cycles and our trained staff of service engineers is ready to convert your existing processors.



PHILIP A. HUNT CHEMICAL CORPORATION

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"Silent" gallbladders... speak clearly to radiologists

Cholecystography consists of radiologic examination following the oral administration of a radiopaque agent (such as TELEPAQUE*) which is excreted by the liver into the bile, and is concentrated in the gallbladder. This concentration provides highly contrasted gallbladder shadows and often obtainable clear definition of the ducts. Evidence indicates cholecystography should be a routine addition to any gastrointestinal "work-up" you order for your patient, to help unmask "silent" gallstones or other gallbladder pathology.

The single most important attribute of any cholecystographic contrast agent is its accuracy in diagnosing biliary tract disease. From this standpoint, TELEPAQUE provides the highest degree of diagnostic accuracy, usually with only one dose, and one examination. Nonvisualization means gallbladder disease;

good visualization means a functioning gallbladder—and you can depend on this diagnosis.

But this is only one of the numerous precise radiodiagnostic procedures—many of them perfected during the last few years—now provided by radiologists who can be of invaluable assistance to you and your practice.

Usual dosage of TELEPAQUE—3 Gm. (6 tablets) at night after a light supper.

Tablets are supplied in envelopes of 6, in boxes of 5 and 25 envelopes.

Side Effects are usually mild, and may include nausea, vomiting, diarrhea, cramps, headache, dysuria and, rarely, skin rash, urticaria, pruritus, flushing.

Contraindications are acute nephritis, uremia, and gastrointestinal disorders which prevent absorption of the medium.

Winthrop

PIONEERS IN PRODUCTS FOR RADIOLOGIC DIAGNOSIS

WINTHROP LABORATORIES
New York, N.Y. 10016

This advertisement—one in a series by Winthrop Laboratories as a service to radiology—is now appearing in those medical publications which are widely read by general practitioners and specialists. It is designed to remind them of the many valuable diagnostic services they can obtain from radiologists.

with Telepaque® (iopanoic acid) visualization means a functioning gallbladder nonvisualization means gallbladder disease

"Silent" and "Vague" gallbladders often present diagnostic problems

Diseased gallbladders can be clinically "silent" or "vague" with confusing signs and symptoms, particularly cholecystitis *without* cholelithiasis. Both require the highest degree of diagnostic accuracy. (Of course, those with classic, readily diagnosable symptoms do not present a problem.) Autopsies indicate that approximately eleven per cent of the population in the United States have gallstones!¹ While females in the "4F" category—*fair, fat, forty and fertile*—are the most frequent victims, the disease is also quite common in males. Delay in diagnosis with resultant delay in employing appropriate measures, according to one authority,² "are fraught with disastrous results for the patient."

"High diagnostic accuracy makes Telepaque the contrast agent of choice"

This is why TELEPAQUE with its unexcelled record of accuracy of 98.3% to 100% in large scale studies, has long been the oral contrast agent of choice in cholecystography and cholangiography.

TELEPAQUE helps you to establish the *functional* status of the gallbladder based on the *concentration* of the medium in the gallbladder—rather than by a *passive* filling of the organ by the agent. This highly important diagnostic attribute has been widely demonstrated by the superb degree of contrast obtained with TELEPAQUE often with only a "one dose, one examination" routine, so that visualization means a functioning gallbladder, nonvisualization means gallbladder disease. *And you can depend on what your films show.*

FOR COMPLETE PRESCRIBING INFORMATION, CONSULT THE PACKAGE INSERT.

Side Effects: TELEPAQUE has low toxicity, and side effects are usually mild. Gastrointestinal effects (diarrhea, cramps, nausea, vomiting) are the most common. Usually the diarrhea is mild, consisting merely of a few loose stools, although in isolated cases it may be severe. Other side effects reported include dysuria (stinging or pain on micturition), headache and, on rare occasions, skin rash, urticaria, pruritus, and flushing.

Contraindications: Acute nephritis, uremia, and gastrointestinal disorders that prevent absorption of the medium.

Supplied: Tablets of 500 mg., envelopes of 6 tablets, boxes of 5 and 25 envelopes; also bottles of 500.

1. Newman, H. F., and Northup, J. D.: *Internat. Abst. Surg.* 109:1, 1959.

2. Weiss, S. (New York Polyclinic Medical School and Hospital): *Clinical Lectures on the Gallbladder*, Yearbook Publishers, Chicago, 1944, pp. 137, 149, 229.

Telepaque®

for precise oral cholecystography
and cholangiography

brand of **iopanoic acid**

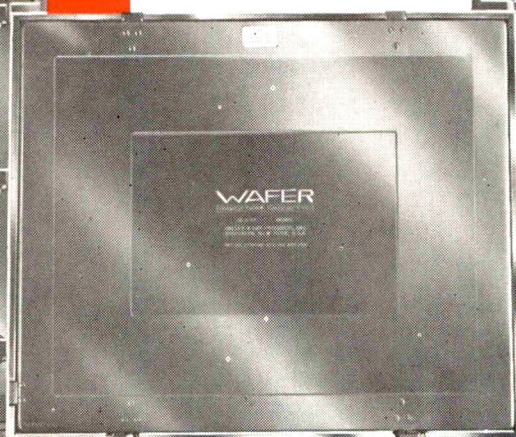
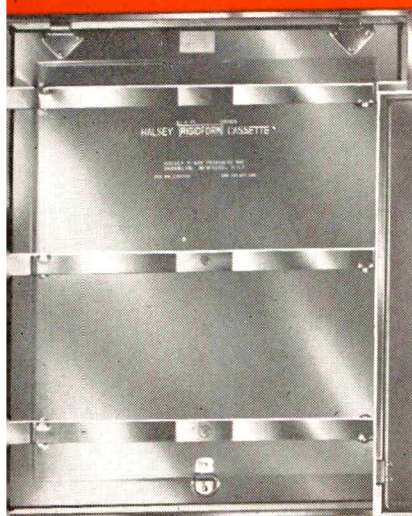
Winthrop PIONEERS IN PRODUCTS FOR RADIOLOGIC DIAGNOSIS

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BARNES-HIND BAROTRAST®

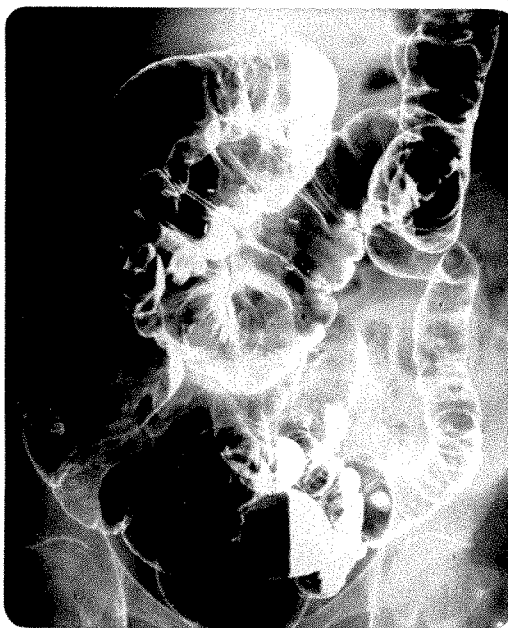
□ Barotrast suspends easily—and **stays** in suspension. Coverage is complete...coating is thin, elastic, tenacious...flow is steady, consistent, and columnar. Barotrast is ideal for routinely precise examinations. □ BAROTRAST® (Specially compounded and micro-nized form of barium sulfate) □



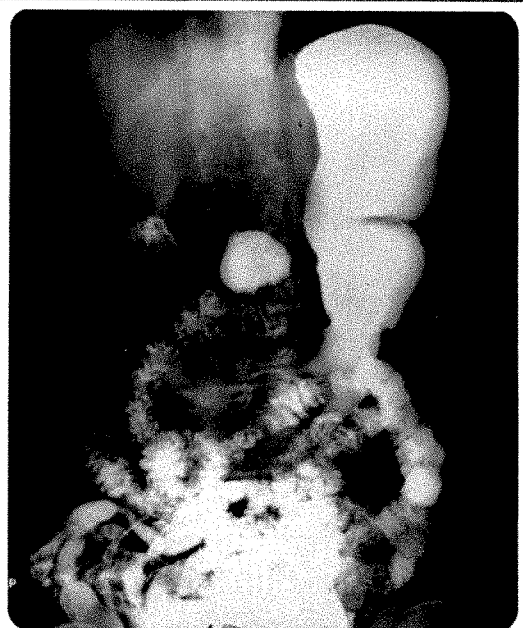
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DIVISION OF BARNES-HIND PHARMACEUTICALS, INC.
Sunnyvale, California



the original
high-density barium product
for unsurpassed delineation



Barotrast used in an air contrast study of the mid transverse colon.



Barotrast used in an upper GI study of the stomach.

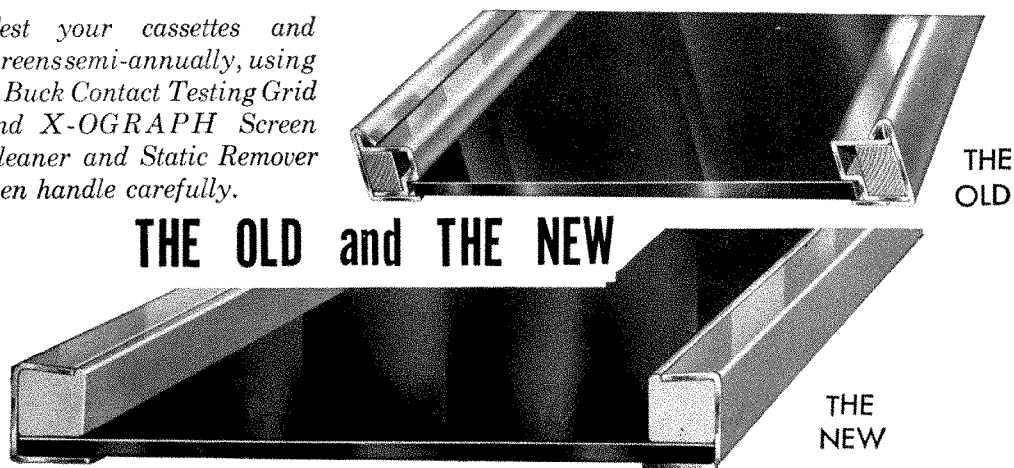


BARNES-HIND BARIUM PRODUCTS
DIVISION OF Barnes-Hind Pharmaceuticals, Inc.
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KNOW YOUR CASSETTE

A CASSETTE is an x-ray accessory item of vast importance - - in fact it should be considered as the most important of any one of the numerous x-ray accessory items.

Test your cassettes and screens semi-annually, using a Buck Contact Testing Grid and X-OGRAPH Screen Cleaner and Static Remover then handle carefully.



Special Points of Interest

- 1—Has no welds to buckle or warp due to temperature change.
- 2—No wood is used in the construction of ALL-PURPOSE CASSETTES.
- 3—Light-tight at all corners when properly loaded.
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- 5—This new cassette has been designed to take the place of the old cassette which we believe it is sure to do.

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ST. LOUIS 36, MO.

X-Ray accessories for those who demand quality

TO KNOW THE DOSE
TO CONTROL THE EFFECT
TO MAINTAIN THE STANDARD

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For Radium Therapy—Dose determinations.

For Radiography—Evaluation standards.

A human-like patient for training.

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For Research in any Radiological Field—Human equivalence
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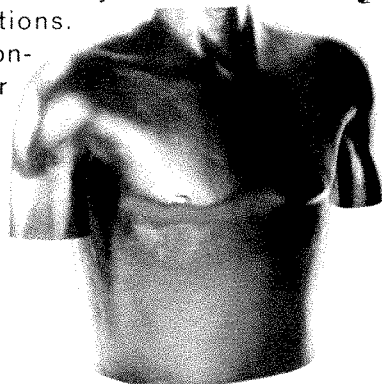
IDO Phantom (Radiation Analysis Dosimetry) A generalized teletherapy patient duplicating the essential features of head and trunk, with a partial human skeleton, lungs and bones. It is sectioned transversely for dose measurements employing film, miniature ion chambers, thermoluminescent tubes. Segments are drilled in standard or special grid holes for meters. Available as average or woman, with accessories for simulating specific patients.

Using the RANDO Phantom, the radiotherapy department can make known isodose curves and can define dose distributions for the most sophisticated treatment plans. It is applicable to individual treatment problems as well.



Sectional Radiographic Phantoms

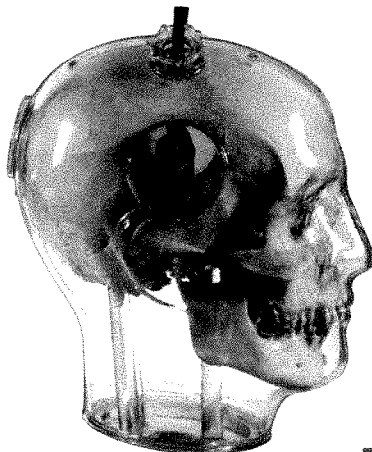
A group of sectional phantoms to serve as reference standards for the diagnostic department. Precise radiographic equivalence to the human body; extremely durable and radiation-resistant . . . for set-up and adjustment of equipment, evaluation and development of techniques, and many other applications. Circulating contrast media for use with cine systems.



Phantom Patient

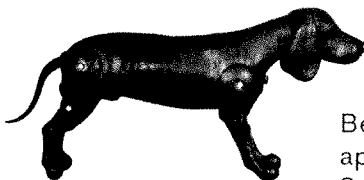
Complete, articulated body to yield human-like radiographs with standard human technical factors. Natural human skeletons, precisely human-equivalent lungs and soft tissues, hollow organs and arterial tree for training with contrast media.

Unlimited radiography permitted for teaching of radiologic technicians . . . Radiographic quality permits assessment of student performance.



Scanning Phantoms

Head Phantom with hollow brain tumors. Abdominal Phantom, with separate hollow organs and hollow or solid tumors; for scanner calibration, confirmation of diagnoses.



For information on radiation-equivalent reproductions, from Astronauts to

Beagles, as well as for data on all general phantom applications, write The Machlett Laboratories, Inc., Springdale, Connecticut 06879.



THE MACHLETT LABORATORIES, INC.

A SUBSIDIARY OF RAYTHEON COMPANY

People make the difference



“he remained the entire night”

a story true and heartwarming

As luck would have it, our Mr. B., on his regular rounds, found himself in the x-ray department of a large hospital when the Big Blackout hit New York last November.

First we learned of what happened there was in a gracious letter sent by the department chief a few days later. Went like this . . .

“I should like to express the sincere thanks of the Hospital for the extraordinary assistance that Mr. B. gave us the night of the blackout. He remained in the department the entire night and aided us in the emergency care of the patients stranded in the department.”

We're proud, but not surprised: for the people here have a long tradition of rising to emergencies. Don't mean to imply that they're all fitted with angelic wings but, on balance, they're a mighty decent lot. As well as being very capable.

People make the difference at Picker.

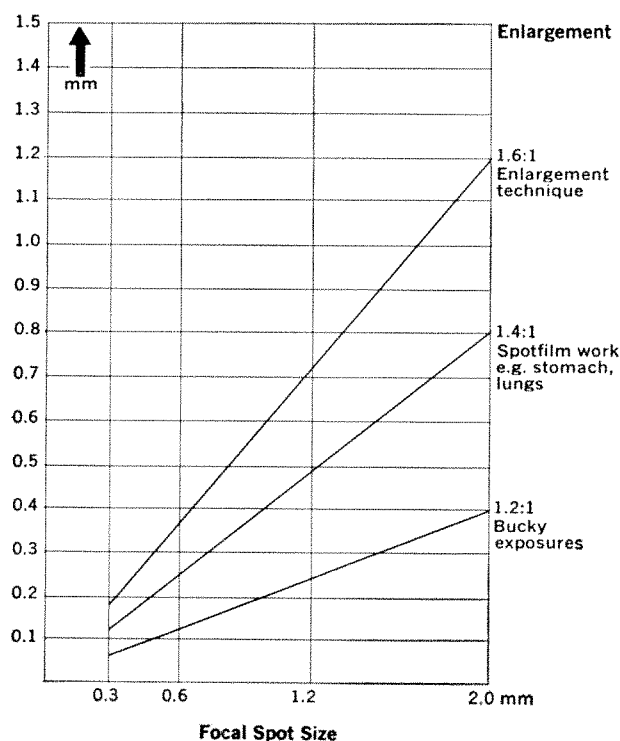
People you can bank on for the best in equipment, in supplies, in maintenance . . . *and in emergencies.*



PICKER X-RAY CORPORATION
White Plains, N.Y.

Ready for work in 0.8 second...

Geometrical
Blurring



A 200 kV Super Rotalix is available for diagnostic purposes. And — the 0.3 and 1.2 Super Rotalix is supplied with a rhenium-tungsten anode to preserve radiographic output.

A fast starter, the Norelco Super Rotalix leaves all other tubes behind in speed — reaching a minimum anode rotation of 8,500 rpm in 0.8 second. The high speed anode rotation of Super Rotalix increases its loadability. Exposures can be made on smaller focal spots than are customarily used—resulting in a significant reduction of geometric unsharpness and unsharpness due to patient motion.

The Super Rotalix performs equally well in all radiographic applications. For thousands of radiologists, the Super Rotalix is the tube for Bucky work, polytomography, normal spot-filming and 70mm spotfilming, pulsed and non-pulsed cine.

The Super Rotalix can produce crisp, sharply defined images in any number of difficult situations:

- When there is a low focus-object/object-film ratio.
- When patient motion is a problem.
- When X-ray magnification is a factor and sharpness must be maintained.

Super Rotalix Focal Spot Combinations: 0.3mm and 1.2mm; 0.6mm and 1.2mm; 0.6 and 2.0.

**HIGH DEFINITION RADIOGRAPHY
IN 0.8 SECOND**

Norelco

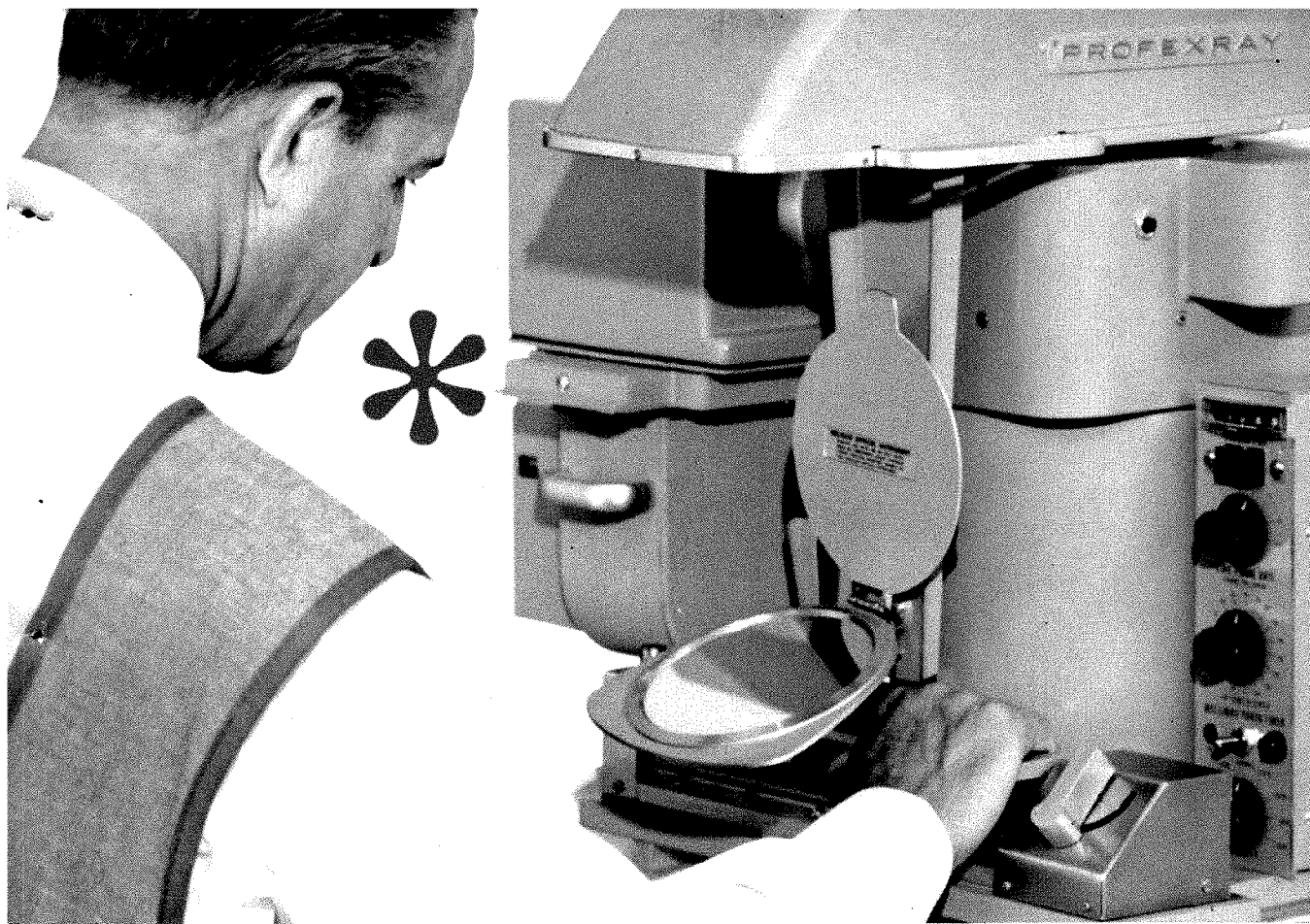
**MEDICAL
EQUIPMENT**

NORTH AMERICAN PHILIPS COMPANY, INC.
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...the NORELCO Super Rotalix







PROFEXRAY ADDS NEW DIMENSIONS TO THE CONCEPT OF **FLEXIBILITY**

EMPEROR 90-360 TABLE—NEW

Heavy-duty, radiographic-fluoroscopic, 180° motor-driven table with tilt range from 90° Trendelenberg through horizontal to vertical.

FLEXIBILITY

1. A wide selection of spot film devices, image intensifiers, intensified image recorders, television systems, cine systems or combinations of these systems has been developed for this table. (Pictured here with PIP-6 Image Intensifier and Intensified Image Recorder.)
2. A true island-type table. Unique design eliminates projections from table body by removing drive motor and transmission from rear of table—results in 360° access to patient.
3. Fluoroscopic and radiographic studies are made easy, using the manual-glide or motor-driven table top, which are available as options.
4. Three smooth motor drives are available: single-speed, dual-speed, or continuously variable speed.



INTENSIFIED IMAGE RECORDER—NEW

Provides records (spot films) of the intensified fluoroscopic image with a degree of definition not obtainable with conventional spot films: (1) at intervals controlled by operator, or (2) sequentially at rates up to six exposures per second.

FLEXIBILITY

1. May be used with or without spot film device—but significant advantages are to be gained when used *in place of* spot film device.
2. Exposure factors to record the fluoroscopic image are 1/10 to 1/20 of those used for regular spot film studies. These lower factors permit the use of a fractional-focus tube, resulting in films of unparalleled sharpness. Magnification studies become routine.
3. A complete range of lenses is available, and these are easily interchanged. 90 mm and 70 mm magazines can be interchanged. Ciné and television cameras are available.
4. May be permanently installed on this table (or Emperor 90-15), with associated options, without necessity of a cumbersome ceiling suspension system.

PROFEXRAY

DIVISION OF LITTON INDUSTRIES



Excretory urogram with Hypaque 50 per cent (30 cc.) Hydronephrosis, right, secondary to cancer of the bladder, blocking the orifice of the right ureter; 25 minute film.

when instrumentation is undesirable precise excretory urography

There are many patients where cystoscopy or catheterization is either undesirable or impossible in determining urinary tract pathology. This may be due to mechanical difficulties (e.g., deformity, anomaly, etc.), debilitated states, infancy, advanced age, infection, pregnancy or after extensive pelvic operations.

In such cases, Hypaque Sodium 50% often provides precisely defined urograms of the kidneys, ureters and bladder, with valuable information about their functional activities, undisturbed by instrumentation. Further advantages are: (1) no age limit to the procedure, and (2) no need to administer an anesthetic.

Contraindications: Advanced renal destruction associated with severe uremia, and severe liver disorders.

Precautions: Caution is advised in patients with hyperthyroidism, hypertension, severe cardiovascular disease, active tuberculosis, and a history of asthma or other allergy, especially to iodine. Because of the possibility of temporary suppression of urine, it is wise to allow an interval of at least 48 hours before repeating retrograde or excretory urography in patients with unilateral or bilateral reduction of normal renal function.

Side effects: Excretory urographic agents may produce symptoms of an anaphylactic* nature in sensitive persons. Patients should be watched carefully during injection as serious reactions, including fatalities, have occurred with all commonly used mediums. Minor reactions, such as nausea, vomiting, excessive salivation, flushing, dizziness, urticaria, and muscular twitching may occur.

Supplied: In sterile aqueous solution. Ampuls of 30 cc. (with 1 cc. test ampuls), boxes of 1, 10 and 25. Also, rubber stoppered vials of 20 cc. and 30 cc., boxes of 1, 10 and 25.

*Physicians should study the package insert for information on preventive measures and management of untoward reactions *before* administering Hypaque (diatrizoate sodium).

Urograms with excellent anatomical detail

Hypaque® Sodium 50%

brand of **diatrizoate sodium**

*an illustrated booklet
with complete information
is available by writing to
Winthrop Laboratories*

Winthrop

PIONEERS IN PRODUCTS FOR RADIOLOGIC DIAGNOSIS

WINTHROP LABORATORIES,
NEW YORK, N.Y. 10016

NEO-CHOLEX POWDER

IMPROVED ORAL
CHOLECYSTOGOQUE

TRY NEO-CHOLEX AT OUR RISK

Order a box of ten doses. Pay the invoice only if you are completely satisfied. With your reorder, we will include a complimentary additional supply. We know that, as a doctor, you will be fair — and we have confidence in the superiority of **NEO-CHOLEX**.

NEO-CHOLEX POWDER is supplied in boxes of ten individual doses with ten disposable cups and lids, for convenience in preparation and administration.



BELL-CRAIG, INC. 41-14 27th Street L.I.C., N. Y. 11101

Visualization of the gallbladder alone, no longer constitutes an adequate roentgen study of the biliary tract. The bile ducts must also be demonstrated (cholecystangiography).

Delineation of these structures is now attainable in 70% to 85% of functioning gallbladders via the fullest utilization of the fat stimulus: effective evacuation and early serial post-fat cholecystograms.

The answer to this problem is **NEO-CHOLEX POWDER** —palatable, well-tolerated, of small bulk, effective, quick-acting, and always ready for immediate use.

DESCRIPTION: **NEO-CHOLEX POWDER** is a palatable, freely dispersing formulation, highly miscible in water, containing hydrogenated vegetable fats, milk solids, lecithin, cocoa and sugar.

ACTION: The action of **NEO-CHOLEX POWDER** in stimulating early and effective contraction in the normally functioning gallbladder is probably in the nature of a hormonal mechanism. Within 10 minutes after administration, the biliary tree is frequently demonstrated, while at 30 to 45 minutes, 75% or more evacuation of the viscus is generally observed.

Early correlation with gastrointestinal studies may also be instituted as **NEO-CHOLEX POWDER** does not interfere with the administration of barium.

INDICATIONS: For use as a gallbladder stimulant replacing fatty foods in routine cholecystography:

1. Prior to dye administration (4 to 6 hours) to counteract biliary stasis in patients who have been avoiding or reducing a normal intake of dietary fat. Failure to evacuate the biliary viscus of inspissated bile in these cases, may result in poor visualization and lead to needless surgery.
2. Following visualization, to indicate the degree of contraction, demonstrate the biliary tree, remove obscuring bile and gas shadows, reveal non-opaque calculi, minute concretions, anomalies, polypoid tumors, adhesions, bands and other conditions which may be rendered visible only after contraction of the viscus.

ADVANTAGES TO PATIENT: **NEO-CHOLEX POWDER** is a welcome substitute for the fatty meal since many gallbladder patients are intolerant of such fats. The product minimizes the disagreeable symptoms of bloating, nausea and vomiting, and solves the problem of aversion many patients possess for fatty foods.

ADVANTAGES TO TECHNICIANS: **NEO-CHOLEX POWDER** is equally welcomed by technicians because of its convenient, ready-to-use nature and ease of mixing. The preparation requires no glasses, spoons or hand-stirring.

ADVANTAGES TO ROENTGENOLOGIST: **NEO-CHOLEX POWDER** insures satisfactory results with a minimum of time loss and inconvenience; affords positive knowledge that directions have been followed; permits early roentgen examination of the gastrointestinal tract.

PROCEDURE: For bile duct demonstration, films are exposed 8-10 minutes post cibum. For contraction of the viscus, at 40 minutes p.c. Best results are obtained by placing the patient on his back with a 20-30° rotation to the right, so that the plane of the duct system lies at right angles to the central ray, as quite often the common duct overlies the spine.

THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

Vol. 97

JULY, 1966

No. 3

ANGIOGRAPHIC AND PNEUMOENCEPHALOGRAPHIC FEATURES OF HOLOPROSENCEPHALY*

By LAWRENCE H. ZINGESSER, M.D., MANNIE M. SCHECHTER, M.D.,
and ASUNCION MEDINA, M.D.
NEW YORK, NEW YORK

THE study of the vascular and encephalographic changes in children with cerebral malformations is a field of special interest within the domain of neuroradiology. This interest is generated by two special considerations. The first of these considerations is that the departures from normal anatomy, particularly those changes from normal vascular anatomy, offer the interested observer some clues about the nature of the pathogenetic mechanisms involved in the production of the malformation. The development of the vascular supply to the brain has been recorded by Padget²⁴ among others, so that informed guesses may be made about the embryologic chronology of a particular malformation involving the parenchyma and vascular supply. This may properly be done without seeking cause and effect relationships, although such speculation may at times lead to attractive hypotheses. The second consideration, of less basic and of more prac-

tical concern, is that the application of neuroradiologic studies to retarded infants allows diagnosis and formulation of a prognosis. Prognosis is of great importance in this field for it determines management of both the patient and the patient's parents.

There are several areas in the field of malformations of the nervous system where the radiologist may be of aid to his colleagues if he acquaints himself with the vascular and ventriculographic or myelographic features of the malformation in question through a reading of the available radiologic and pathologic literature. There are other areas, however, where no complete description of these changes exists. The spectrum of holoprosencephaly is one such area. There has been only 1 report on the angiographic features of holoprosencephaly, and there have been only a few reports on the radiologic aspects of the ventricular anatomy. The neuropathologic literature contains much informatin about the

* Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October 1, 1965.

From the Departments of Radiology and Neurology, Albert Einstein College of Medicine, New York, New York.

This work was supported in part by a Special Traineeship (B.T. 937) from the National Institute of Neurological Diseases and Blindness, Public Health Service.

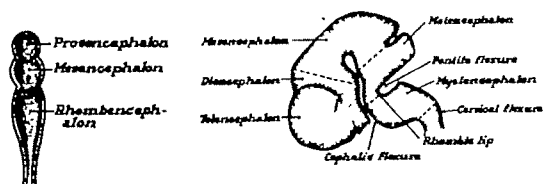


FIG. 1. The drawing on the left shows the 3 primitive vesicles of an early human brain. The drawing on the right is that of an older embryo showing the flexures and secondary vesicles. The telencephalon and diencephalon are the secondary vesicles resulting from a constriction of the prosencephalon.

clinical, gross, and microscopic features of the malformation but only a little about the vascular anatomy.

TERMINOLOGY AND HISTORIC BACKGROUND

Since the term "holoprosencephaly" may be unfamiliar to many radiologists, it is proper that we begin with a definition and with a short history of the entity. "Holoprosencephaly" literally means "total" or "entire" prosencephalon. The prosencephalon is the part of the developing brain which gives rise to the telencephalon and diencephalon (Fig. 1). The term "holoprosencephaly" was proposed to specify certain malformations characterized by a fusion of the telencephalic and diencephalic portions of the two cerebral hemispheres, but the term is also used to include certain other malformations involving these areas, particularly those involving the olfactory apparatus.

According to Gauthier,¹⁸ the first report on a malformation of the sort we are concerned with was made by Rudius in 1588. In a review of the subject published in 1960, Gauthier counted 61 reports on this entity in the literature over the years, and retained 52 of these reports which he felt had complete enough information to certify themselves as valid cases. Cases reported by others and uncounted in Gauthier's series bring the total of reports to somewhere around a hundred cases. In 1882, Kundrat¹⁹ titled the entity that we are concerned with "arhinencephaly." However, as Yakovlev²⁸ pointed out on his paper on the pathoarchi-

tectonic studies of cerebral malformations, the term "arhinencephaly" (implying agenesis of the entire rhinic lobe of the brain) is a misnomer. According to Yakovlev, pathoarchitectonic studies show that the anterior median cortex of the brain of the holosphere is homologous with the gigantopyramidal area of the normal brain (even though the pyramidal tracts are absent), and caudally the cortex of the holosphere is homologous with the parietal, occipital, and temporal lobes of the normal brain. Thus, according to this analysis, the anterior frontal lobes are not present in this sort of brain. The hippocampi, though, are present as distinct cytoarchitectural regions. The hippocampi are found in a more dorsal position than usual. Yakovlev substituted the term "holotelencephaly" for "arhinencephaly," and recently a more inclusive term—"holoprosencephaly"—has been suggested by DeMyer and Zeman.¹² They, in defending the term "holoprosencephaly," stated: "The customary term arhinencephaly places undue stress on only one of the many cerebral defects and seems to connote the erroneous assumption that absence of the olfactory bulbs and tracts is the cause of the cerebral malformation. Moreover, some brains which unquestionably belong to this teratologic series have olfactory bulbs and tracts. The alternate term cyclencephaly is likewise unsatisfactory since it is limited to the more severe forms of arhinencephaly, where the cerebrum is undivided into hemispheres. The term holotelencephaly has the virtue of previous usage (Yakovlev) but does not reflect any of the defects of diencephalic tectogenesis often found such as incomplete cleavage of the thalami, colobomas, or anophthalmia. . . . Holoprosencephaly . . . implies a tendency for the prosencephalon to remain whole as a single, simple, more or less undifferentiated bulb, incompletely cleft into complex cerebral hemispheres. If holoprosencephaly is used as the generic term for the teratologic series, the term arhinencephaly can be reserved for its specific meaning, absence of the olfactory bulbs and tracts."

TABLE I

RELATIONSHIP BETWEEN FACIAL CHARACTERISTICS, CLINICAL CHARACTERISTICS AND BRAIN MALFORMATIONS WITHIN THE SPECTRUM OF HOLOPROSENCEPHALY

Face	Brain	Clinical
Cyclopia	Alobar holoprosencephaly	Lethal
Ethmocephaly	Alobar holoprosencephaly	Amentia, lethal
Cebocephaly	Alobar holoprosencephaly	Amentia, lethal
Median cleft lip and palate	Usually alobar holoprosencephaly	Amentia, lethal
Median philtrum-premaxilla anlage	Semilobar or lobar holoprosencephaly	Amentia; some survive into childhood
Normal	Semilobar or lobar holoprosencephaly	May survive infancy and childhood; some are amented; some are eunuchoid

MALFORMATIONS ASSOCIATED WITH HOLOPROSENCEPHALY

There is a spectrum of malformations within the category of holoprosencephaly in which failure of prosencephalic cleavage is the common denominator (Table I). According to DeMyer and Zeman, cases in the category under discussion tend to fall into fixed subdivisions; although there are transitional forms, most cases can be rather clearly categorized. The most severe of these malformations is cyclopia (Fig. 2, *A* and *B*). Here there is a single orbit with a proboscis above the orbit. The nasal bones, ethmoidal bones, vomer, lacrimal bones, turbinates, and premaxilla are absent. The maxillae are underdeveloped and are often fused. The frontal bone is narrow, is frequently single, and is sometimes keel-shaped. The metopic suture may be prematurely obliterated. Not uncommonly, the frontal bone originates from a single midline ossification center. The anterior cranial fossa is small. The sphenoid is underdeveloped, and there is only one optic canal. The optic nerve may or may not be present. The olfactory nerves are absent. The head is usually small. The forebrain is single, and the lateral ventricles are fused so that there is a single ventricle which communicates freely with the third ventricle.

The next most severe form is ethmocephaly. Here there are 2 orbits, but the nose is absent or is replaced by a trunk (proboscis).

The forehead is small and the frontal suture is obliterated. The nasal bones, premaxilla, septum of the ethmoid, and turbinates are absent. The lacrimal and palatine bones are fused. The optic nerves bifurcate at the dura after a single origin.

Cebocephaly comes next in the spectrum. A flat rudimentary nose is present in its normal position. Again, there is a keel-like protrusion of the forehead. The sphenoid is small and short and the ethmoids are defective. The optic foramina lie close together in a common bony canal which is divided only by a membrane. The nasal septum and the premaxilla are absent. The maxillae are fused. The forebrain is simple.

Next comes a form of holoprosencephaly associated with a median cleft-lip. Here the philtrum is missing and this gap is confluent with a single nasal opening. The nose is flat, and there is hypotelorism. There is a cleft-palated and a keel-shaped forehead. The premaxilla, nasal septum, horizontal plate of the ethmoid, and crista galli are absent. As in cebocephaly, the optic foramina are jointed. The small frontal bone is divided, or through a fusion of the ossification centers, it is single. In this form of holoprosencephaly, as in all of the preceding forms, the underlying brain malformation is alobar holoprosencephaly.

A still milder form of holoprosencephaly is labeled holoprosencephaly with median philtrum-premaxilla anlage. Here again orbital hypotelorism is present. There is a

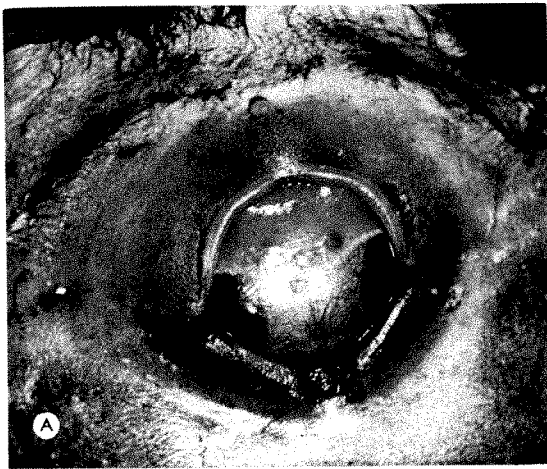


FIG. 2. (A) The orbit and orbital contents of a cyclops are shown. Note the single globe and double iris, the small proboscis above the upper lid, and the single eyebrow. A single large optic foramen was present in this patient. (B) Brain of same patient. O indicates the optic chiasm. C indicates the cerebral mantle, which is little more than a sac enclosing a monoventricle. The cerebellum and brain stem are fairly well developed. The basilar artery and its branches are normal, but vessels of the anterior circulation are very irregular in appearance.

bilateral cleft of the lip with a median process representing the philtrum-premaxillary anlage. There is a flat nose. Here the brain malformation is semilobar or lobar holoprosencephaly. Semilobar and lobar refer to the fact that there is only partial fusion of the forebrain.

Then there are forms of semilobar or lobar holoprosencephaly without facial malformations. Olfactory bulbs and tracts may be present. The corpus callosum may be absent. These patients may have normal intelligence. Some are eunuchoid.

Kundrat has suggested that we include in this series of malformations brains with aplasia of the corpus callosum (even though the olfactory system is normal). This may be logical in some cases, especially when the aplasia of the corpus callosum is associated with a dorsal cyst communicating with the third ventricle. It is not easy, however, to include most cases of agenesis of the corpus callosum within this category.

ETIOLOGY

There are a few points to be made about the etiology of holoprosencephaly. The prosencephalon is induced by the foregut and intervening mesodermal tissue between the foregut and the forebrain. In holoprosencephaly the neural defects are most severe in the prosencephalon, especially the structures developing in or near the commissural plate at the rostral end of the third ventricle. Experimentally, it has been shown that interference with the zone of entomesodermal tissue between the foregut and the prosencephalon can produce median defects of the face, hypotelorism, cyclopia, and holoprosencephaly.

Holoprosencephaly in association with facio-nasal malformation has been observed in a study of guinea pigs by Wright and Wagner,²⁷ in 1934. Cowen and Geller⁶ have found that irradiation of pregnant rats on the 14th to 17th days of gestation will produce aplasia of the corpus callosum with formation of a dorsal cyst extending upward between the hemispheres from the roof of the third ventricle. Binns *et al.*³ found that alobar holoprosencephaly occurred in lambs where the ewes producing the lambs ingested a toxic plant—*Veratrum californicum*.

Chromosome studies on some of the patients with alobar holoprosencephaly (Fig. 3) have shown trisomy 13-15, while other

children with this malformation had had a normal karyotype. When trisomy 13-15 is present, extracerebral and extracranial defects are associated.

In addition to radiation and chromosome abnormalities, other etiologic possibilities suggested for human holoprosencephaly are: diabetes mellitus, toxoplasmosis, syphilis, and rubella.

DIAGNOSTIC PROCEDURES

Among the diagnostic procedures (other than radiologic) which may be helpful are transillumination—one is able to visualize the monoventricle, and electroencephalography—here one finds multiple independent spikes, paroxysmal hypersynchrony, and usually flattening of the waves over the area of the monoventricle.

ROENTGENOLOGIC FINDINGS

PLAIN ROENTGENOGRAPHY

The absence of and/or fusion of various cranio-facial bones in the spectrum of holoprosencephaly has been mentioned above. It is appropriate at this point to mention the work of Currarino and Silverman.⁷ They have standardized interorbital measurements and they discuss the relationship between the orbital hypotelorism, trigonocephaly, and "arhinencephaly." Hypotelorism is more often obvious roentgenographically than clinically and is a frequent finding in holoprosencephaly and in trigonocephaly. Others have indicated that a normal interorbital distance and even hypertelorism may be seen in holoprosencephalics.¹² Trigonocephaly is a cranial anomaly in which the frontal bone is small, narrow, and pointed and in which the metopic suture is prematurely obliterated, partially or completely. Trigonocephaly can occur in association with holoprosencephaly or as an isolated lesion.

The plain roentgen findings of holoprosencephaly were discussed at the VII Symposium Neuroradiologicum in 1964 by Campbell and co-workers, and a paper on this subject by that group will soon be published.²⁰



FIG. 3. Two month old microencephalic child with alobar holoprosencephaly. The mother had rubella in the first trimester of her pregnancy. Hypotelorism is present, although this is more obvious roentgenologically than clinically. The nose has a flat bridge. The palate and lip have a median cleft. Trigonocephaly is present although this is not obvious in the photograph.

PNEUMOENCEPHALOGRAPHY

Air studies which were performed on patients probably falling within the spectrum of holoprosencephaly have been reported by: Brenner,⁵ 1939; Bannwarth,¹ 1939; Davidoff and Epstein,⁸ 1950; Zellweger,²⁹ 1952; Mosberg and Voris,²¹ 1954; Decker,⁹ 1960; and Wisen *et al.*,²⁶ 1965. If agenesis of the corpus callosum associated with an interhemispheric cyst is included in the holoprosencephalic spectrum, then air studies on such cases have been reported by Foerster,¹⁶ 1939; Oftedal,²³ 1959; and Zinggesser *et al.*,³⁰ 1964.

The hallmark of holoprosencephaly on air study is fusion of the lateral ventricles. The ventricles together may be small, normal, or large in size (in proportion to the surrounding parenchyma). Although microcephaly is usually present, macrocephaly exists within the spectrum. Absence of the falx and retroversion of the cerebrum are other findings which may be seen on air studies.

Conditions which may be confused with holoprosencephaly on air studies are hy-

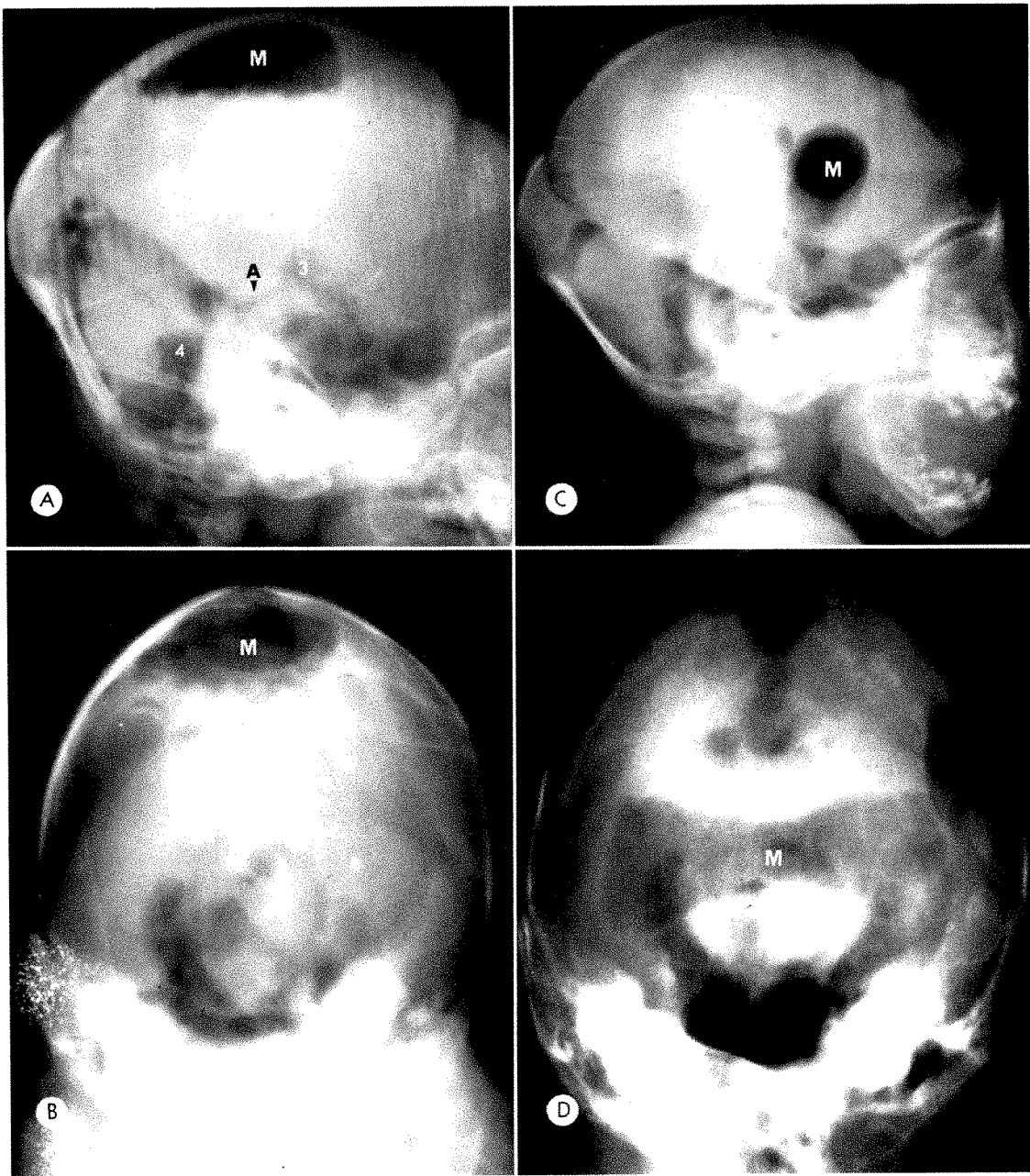


FIG. 4. (A) Lateral roentgenogram of a pneumoencephalographic series in a sitting position. Same patient as in Figure 3. Air can be seen around the spinal cord, in the cisterna magna, around the cerebellum in the fourth ventricle (4), in the aqueduct (A), posterior third ventricle (3), and in the monoventricle (M). The configuration of the anterior portion of the air in the monoventricle is a feature that differentiates this from a dilated lateral ventricle. (B) Companion roentgenogram (reverse Towne projection) to A. The collection of air (M) in the monoventricle is in the midline. Note that no falx is outlined here. (C) Brow-up lateral roentgenogram in the pneumoencephalographic series. M represents air in the anterior portion of the monoventricle. There is retained air around the spinal cord, cerebellum, and cerebrum. Practically no cerebral retroversion is present. Some air is present in the fourth ventricle as well. (D) Companion roentgenogram (anteroposterior Towne projection) to C. M indicates the anterior extent of the monoventricle. Some air is present over the cerebral tissue in the midline and on the left.

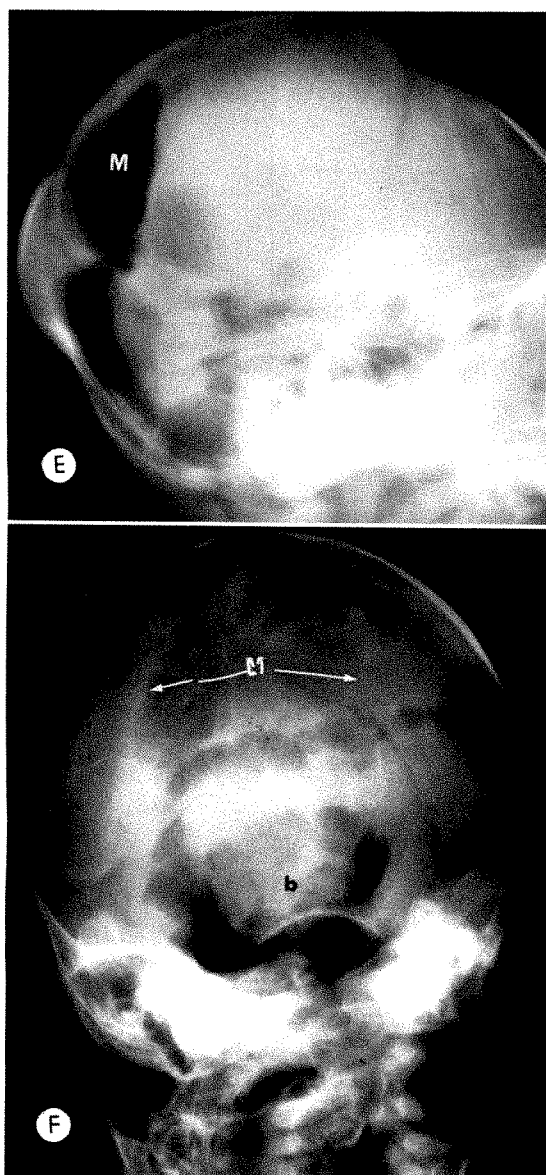


FIG. 4. (E) Brow-down lateral roentgenogram in the pneumoencephalographic series. M represents the monoventricle. The large collection of air below is posterior to the cerebellum. (F) Companion roentgenogram (reverse Towne projection) to E. M represents the midline monoventricle. There is considerable air around a small brain stem (b).

drancephaly and absence or perforation of the septum pellucidum. In hydrancephaly there are no cerebral hemispheres for all practical purposes. Furthermore, a falx is present in hydrancephaly. For these reasons, the air study of a hydrancephalic can

easily be differentiated from the air study of an alobar holoprosencephalic.

There is apt to be more confusion in diagnosis between absence of the septum pellucidum and semilobar or lobar holoprosencephaly. According to Davidoff and Epstein,⁸ the first report of congenital absence of the septum pellucidum was made by Tenchini in 1880, and Dyke and Davidoff¹⁵ were the first to report a case diagnosed during life by encephalography (1935). In the case presented by Davidoff and Epstein⁸ in their book, the brow-up roentgenograms show an absence of the septum pellucidum with the third ventricle in normal position. They also present 2 cases with a "single lateral ventricle." These are hydrocephalics showing a large single centrally placed cavity in place of two lateral ventricles. The large cavity in one seems to have clover-leaf shape and the central leaf of the clover extends up to the wall of the skull. Davidoff and Epstein's explanation that these appearances are due to hydrocephalus plus congenital absence of the septum pellucidum is disputed by Zellweger,²⁹ who points out that the posterior and inferior parts of the lateral ventricular system are fused along with the anterior portion.

Some cases of absence of the septum pellucidum, especially when associated with other anomalies such as agenesis of the corpus callosum will be impossible to differentiate from holoprosencephaly by means of air studies (and pathologically?).

Included in our report are roentgenograms from two encephalographic studies of patients within the spectrum of holoprosencephaly. The first of these patients had the alobar form of holoprosencephaly (Fig. 4, A-F). Note that the first two roentgenograms of the series show a normal fourth ventricle. The air rises into the monoventricle—the so-called "dorsal cyst," which is the posterior part of the single ventricle. No falx is outlined. Brow-up roentgenograms demonstrate a fused ventricular system, and in the case represented there are extensions bilaterally which appear to be incompletely developed frontal horns. The second

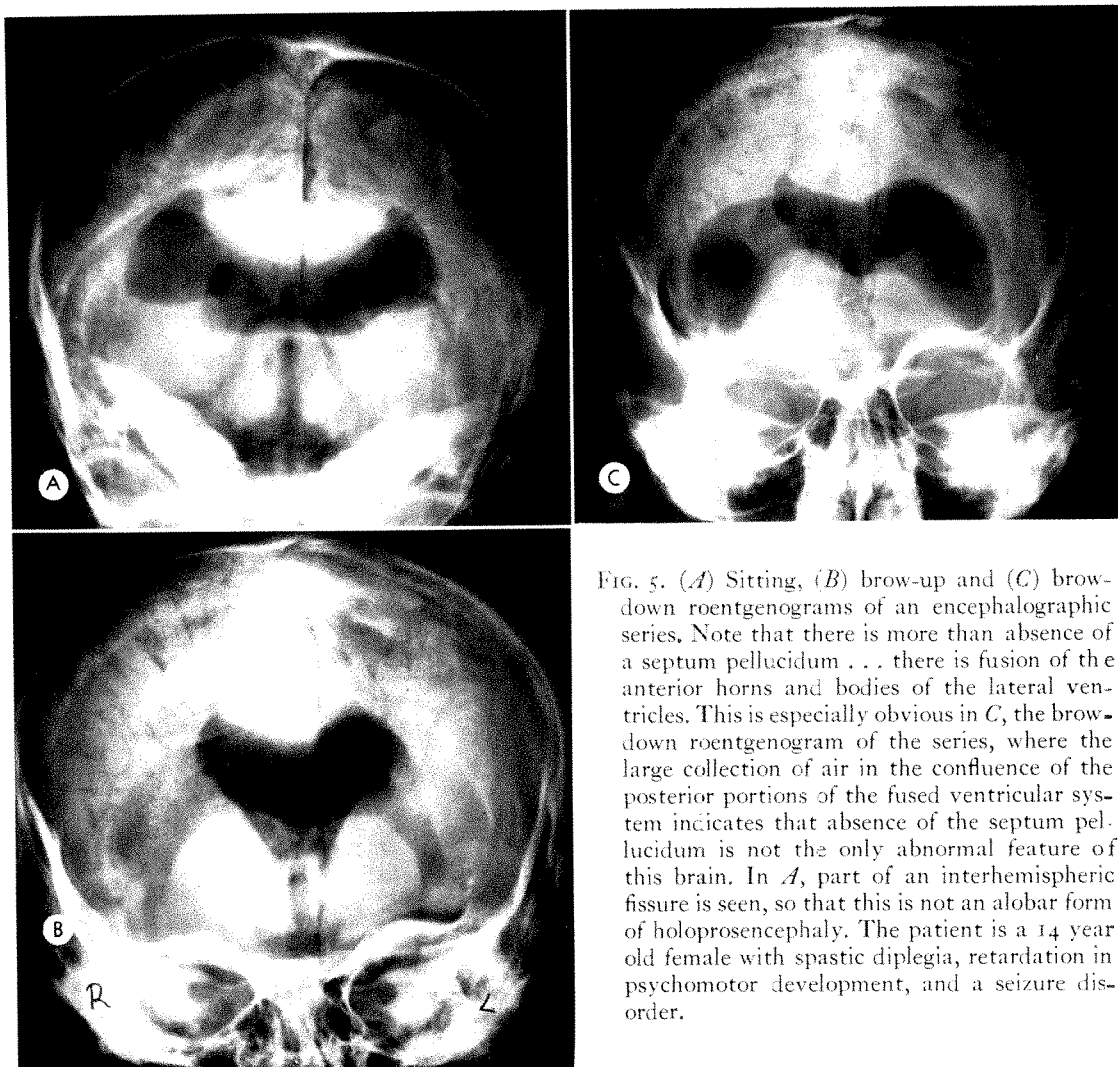


FIG. 5. (A) Sitting, (B) brow-up and (C) brow-down roentgenograms of an encephalographic series. Note that there is more than absence of a septum pellucidum . . . there is fusion of the anterior horns and bodies of the lateral ventricles. This is especially obvious in C, the brow-down roentgenogram of the series, where the large collection of air in the confluence of the posterior portions of the fused ventricular system indicates that absence of the septum pellucidum is not the only abnormal feature of this brain. In A, part of an interhemispheric fissure is seen, so that this is not an alobar form of holoprosencephaly. The patient is a 14 year old female with spastic diplegia, retardation in psychomotor development, and a seizure disorder.



FIG. 7. (A) Anteroposterior brow-up pneumoencephalogram of a 62 year old male with agenesis of the corpus callosum and an interhemispheric arachnoid cyst which communicates with the third ventricle. The septum separating the cyst from the right lateral ventricle is obvious, but the septum separating the cyst from the left lateral ventricle cannot be seen here. (B) Laminagram of the same patient. Arrows point to the septum separating the cyst from the left lateral ventricle. (C) Right carotid angiogram with compression of the left carotid artery. Both anterior cerebral arteries are present but are abnormally large. They are separated in their A2 portions by the midline cyst. (D) Left lateral carotid angiogram of the same patient. The configuration of the anterior cerebral artery suggests that hydrocephalus is present. (A-D reproduced with permission of the *British Journal of Radiology*.³⁰)

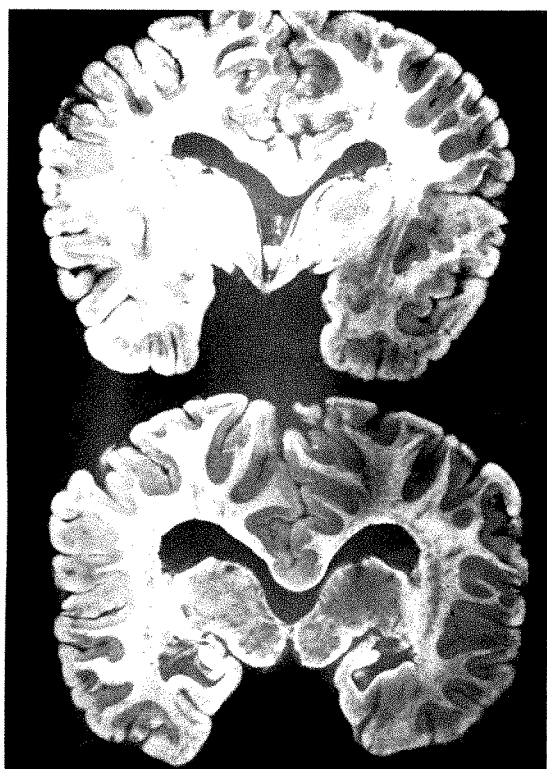
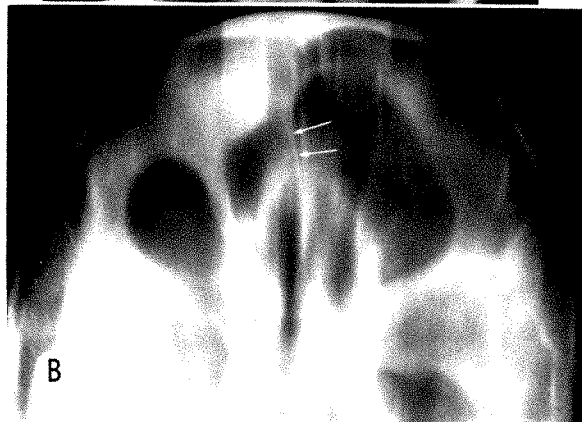
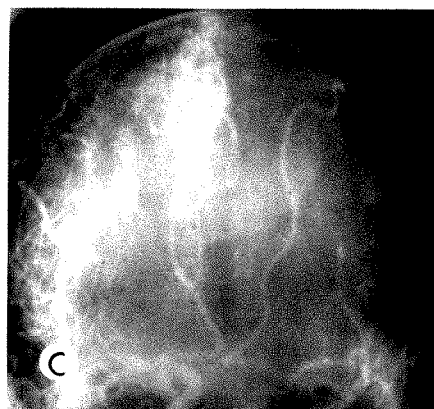
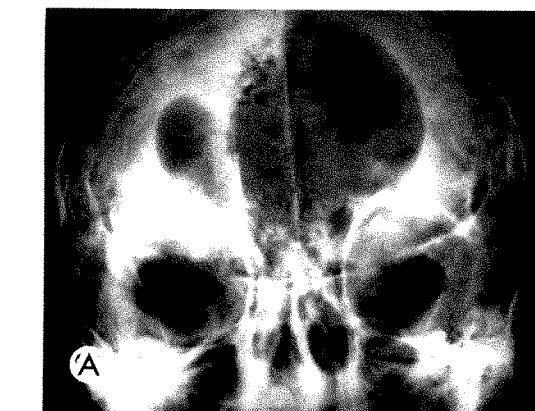


FIG. 6. The upper slice is an anterior section and the lower slice is a posterior section of the brain of a 2 year old female with semilobar holoprosencephaly. Note the similarity of the ventricular configuration to the configuration of the ventricular system of the patient in Figure 5, *A*, *B* and *C*.

set of holoprosencephalic air studies are shown in Figure 5, *A*, *B* and *C*. Here no autopsy proof exists, as the patient is alive at the age of 14 years. Clinically, she has spastic diplegia, retardation in psychomotor development, and a seizure disorder. The child's head is small—below the 10th percentile for a 10 year old. Encephalographic study reveals fusion of the lateral ventricles in part. In spite of the fact that the child has no anosmia, she is considered by us to have a form of holoprosencephaly. Compare the configuration of the ventricular system in this case with the photographs of the brain in Figure 6. This last case is a patient



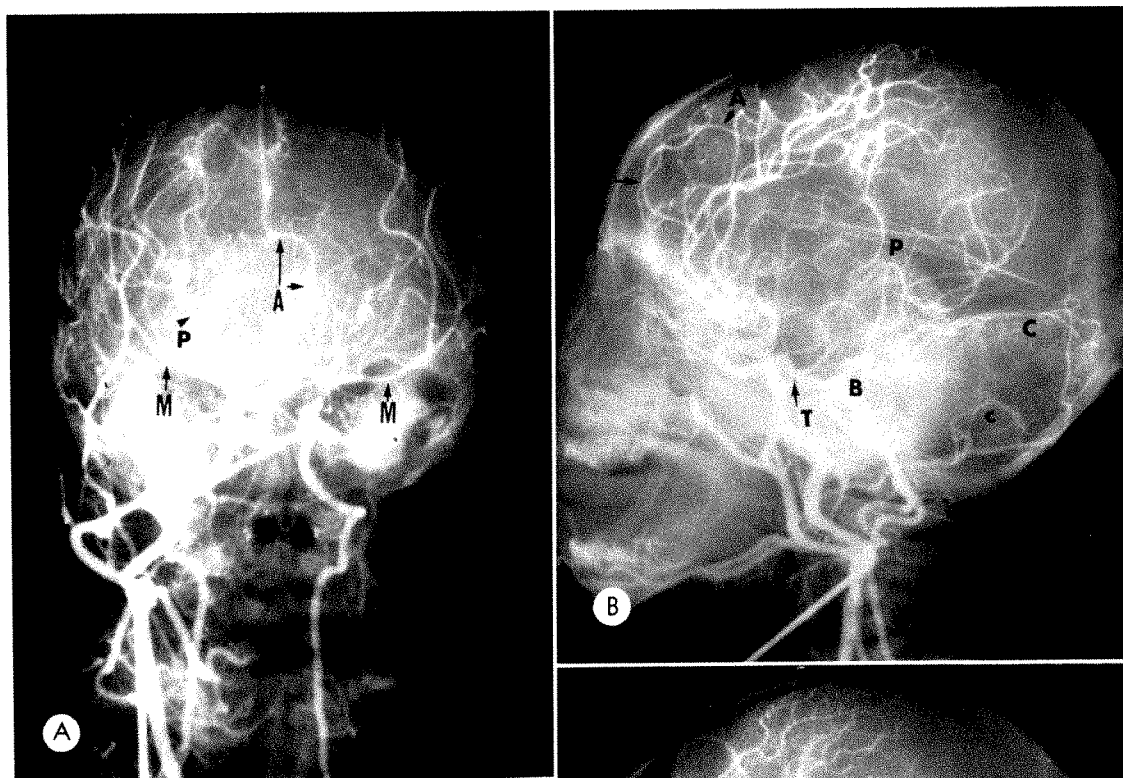


FIG. 8. (A) Same patient as in Figures 3; and 4, A-F. Percutaneous carotid angiogram in the anteroposterior Towne projection. The needle is in the right common carotid artery. Reflux of contrast material has opacified a common trunk for brachiocephalic vessels, but the left carotid artery is not opacified even though it is patent. Both vertebral arteries can be seen. A represents the single anterior cerebral artery which runs over the fused hemispheres to the left of the midline and then runs along the midline over to the area of the monoventricle, seeming to anastomose with the abnormally placed right posterior cerebral artery (P). The left posterior cerebral artery is present but cannot be easily identified. M represents a middle cerebral artery on each side. Superior cerebellar arterial branches are seen between A and P. (B) Lateral carotid angiogram.

T indicates a carotid-basilar anastomosis (primitive trigeminal artery). A is the median anterior cerebral artery. Note the separation of brain from skull indicated by the arrow; a small degree of retroversion is present. P is in the fork of an abnormally placed posterior cerebral artery. B represents the basilar artery. C is a superior cerebellar artery; c is a posterior inferior cerebellar artery. (C) Later phase of the angiographic series. The small arrows indicate the limits of the monoventricle. The monoventricle is delimited mainly by branches of the posterior cerebral arteries.

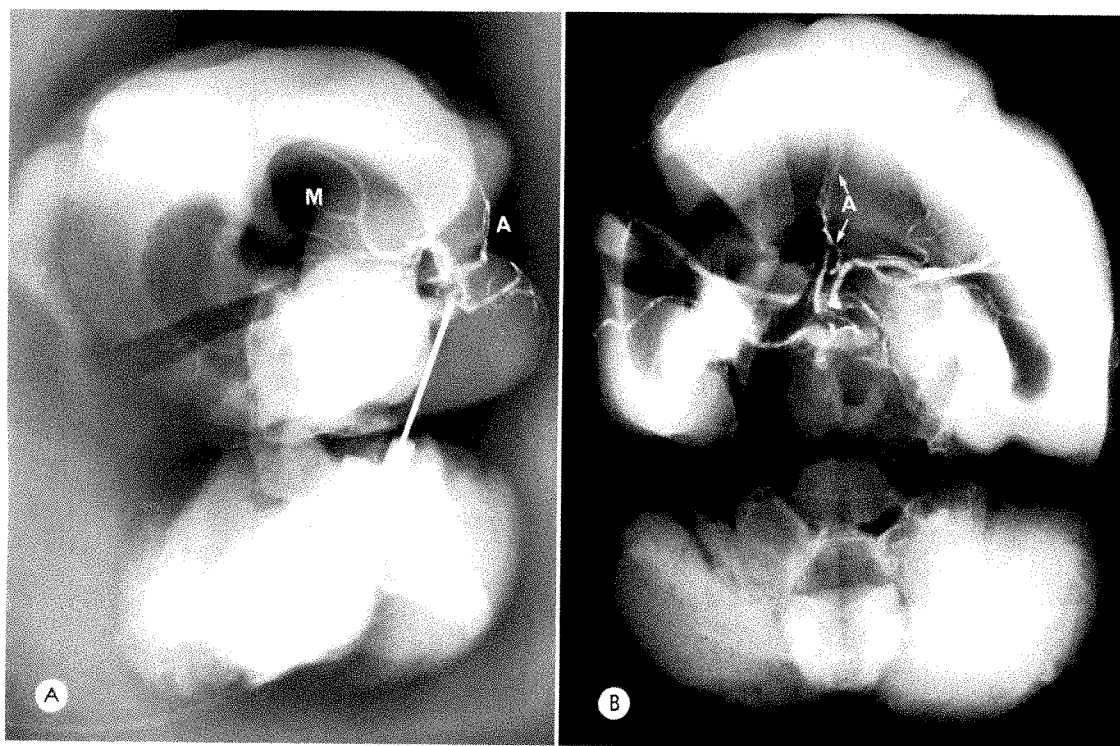


FIG. 9. (A) Lateral and (B) basal views of partially complete postmortem angiography of the patient in Figures 3; 4, A-F; and 8, A, B and C. A is the median anterior cerebral artery. M represents the monoventricle.

about whom little is known clinically. The brain is that of a 2 year old female who had measles and pneumonitis. The pathologic findings are those of semilobar holoprosencephaly.

For purposes of comparison a case of ours previously published³⁰ is presented in Figure 7, A-D. This case may belong in the spectrum of holoprosencephaly.

ANGIOGRAPHY

Yakovlev²⁸ has described the arterial distribution in several (5) brains of children with holoprosencephaly. In brains that would be characterized as showing alobar holoprosencephaly, the anterior circulation is derived from 3 arterial trunks—1 median trunk (the anterior cerebral artery) and 2 lateral trunks (the middle cerebral arteries). He encountered no abnormality in the vertebrobasilar system. He did not report the



FIG. 10. Brain of same patient as in Figures 3; 4, A-F; 8, A, B and C; and 9, A and B. This view from above shows the diencephalic structures at the floor of the monoventricle. Only a portion of the covering of the monoventricle remains. The findings are those of alobar holoprosencephaly.

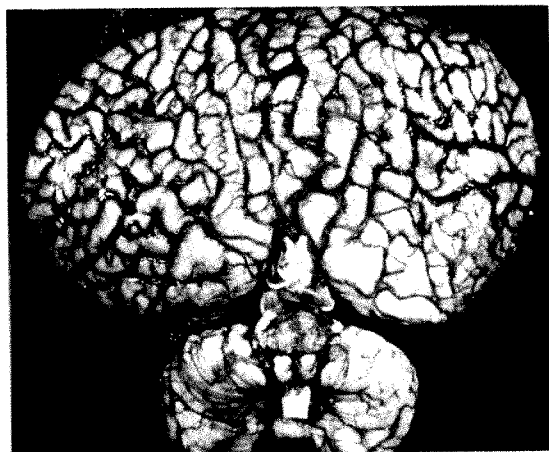


FIG. 11. Outer surface of another alobar holoprosencephalic brain. Ramifications of the median anterior cerebral artery can be seen in the midline, while the middle cerebral arteries are more laterally situated.

arterial distribution in his largest specimen—the brain of a 27 month old child. This last brain is an example of the semilobar type of holoprosencephaly.

Wisén *et al.*²⁶ have recently reported the findings noted in the cerebral angiograms (obtained via an arch study) of a 4 month old child with alobar holoprosencephaly; no homologues of the anterior cerebral arteries were found. In some of the other holoprosencephaly brains studied by them at autopsy, 1 carotid artery was hypoplastic

and the other carotid supplied both sides of the brain.

Figure 8, *A*, *B* and *C* shows the angiograms that we obtained percutaneously in the study of a 2 month old child with the alobar form of holoprosencephaly. The angiograms demonstrate a single anterior cerebral artery which has an undulating course over the frontal surface of the brain.

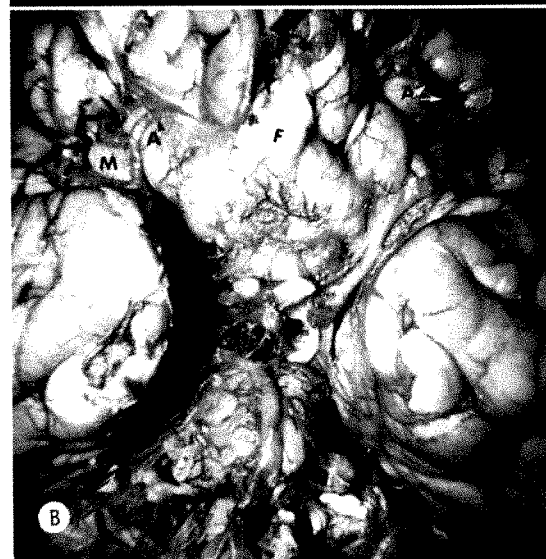
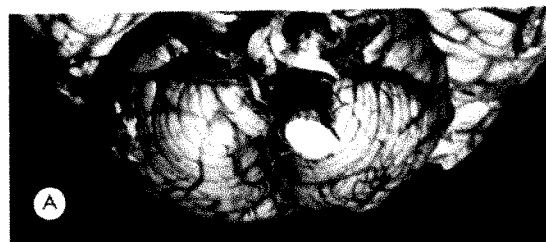
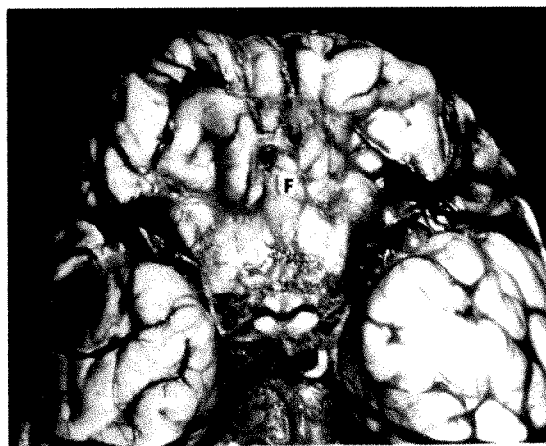


FIG. 12. (*A*) Basal surface of the whole brain of the patient in Figure 6. Note the fusion (*F*) of the hemispheres along the basal surface. This indicates that semilobar holoprosencephaly is present, for an interhemispheric fissure is seen elsewhere. (*B*) Photograph (with higher magnification) of the anterior portion of the brain in *A*. *F* represents the area of fusion. There are 2 anterior cerebral arteries indicated by the *A* with the black arrow and the *A* with the white arrow. Each arises from a branch of the carotid artery. This branch on each side also gives rise to a middle cerebral artery (*M*). From their origin laterally, the anterior cerebral arteries run toward the midline and branch over the poles. Note the difference between this configuration and the configuration of the arteries seen in Figure 7*C*, where the diagnosis is agenesis of the corpus callosum associated with an interhemispheric cyst.

In the lateral view the most striking finding is the relatively avascular area representing the single ventricle. Note also the peculiar course of the posterior cerebral artery. An incidental finding is the persistent trigeminal artery (see also Figure 9, *A* and *B*, the postmortem angiograms, and Figure 10, a photograph of the brain). Figure 11 illustrates the findings in another alobar holoprosencephalic brain.

Although we have not done angiography *in vivo* on a patient with semilobar or lobar holoprosencephaly, the brain specimen we have seen representing semilobar holoprosencephaly shows two anterior cerebral arteries arising from branches of the internal carotid arteries. These branches also give rise to the middle cerebral arteries. Note the pattern of distribution in Figure 12, *A* and *B*, the brain of a child with semilobar holoprosencephaly. Compare this with the pattern seen in a case of agenesis of the corpus callosum with a midline dorsal cyst (Fig. 7*C*).

SUMMARY

A discussion of the spectrum of holoprosencephaly has been presented. Particular attention has been paid to the radiologic diagnosis utilizing air studies and vascular studies.

Lawrence H. Zingesser, M.D.
Department of Radiology
Neuroradiology Section
Albert Einstein College of Medicine
New York, New York

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DIAGNOSIS OF EMBOLIC OCCLUSIONS OF SMALLER BRANCHES OF THE INTRACEREBRAL ARTERIES*

By B. ALBERT RING, M.D.

BURLINGTON, VERMONT

EMBOLIC occlusions of the smaller branches of the intracerebral vessels are well recognized by pathologists,¹⁹ but the application of this condition to cerebral angiography confronts the radiologist with two relatively unfamiliar problems; first, the recognition of the small vessel occlusions and, secondly, the differentiation of emboli from primary thromboses. The purpose of the author is to point out that, in some cases at least, these diagnoses can be made and that the carotid arteries themselves should be held suspect as a source of emboli.

We have previously described the method of applying zones to the termination of the 4 major branches of the middle cerebral artery^{13,14} that we believe is very helpful in recognizing occlusions of branches of this vessel. Since the pericallosal and posterior cerebral arteries are silhouetted relatively free from overlying vessels, careful attention to them throughout their course will usually reveal occlusive lesions, if present. The middle cerebral artery differs only in its complexity so that the actual point of occlusion is often concealed and the origin and course of the 4 major vessels of the middle cerebral artery have so many variants that the only consistent anatomic finding is in their terminal distribution. There is still a general tendency to divide occlusive lesions involving the middle cerebral artery into complete or partial, although Larson and colleagues⁷ further divided the occlusions into those involving the insula branches as opposed to the sylvian. Lascelles and Burrows,⁸ however, in a large series, were able to identify the

individual branches of the middle cerebral artery involved in the occlusive process. Although no claim is made that all branch occlusions can be recognized angiographically, we believe that it is of practical rather than academic importance to attempt to ascertain the occlusion or patency of every individual branch of the middle group, since, without some effort to do so, occlusions of sizable and significant branches may be missed altogether.

The zones of termination of the 4 main branches of the middle cerebral artery may be roughly outlined as follows: A line is drawn parallel and 1 inch from the inner table of the skull. Another line is drawn through the axis of the sylvian vessels to the region of the tuberculum sellae; from this point a line is drawn posteriorly to the point corresponding to the internal occipital protuberance and from here to the mid-point of the sylvian line. Another line upward from this point, parallel to the coronal suture, completes the diagram. The largest and most anterior area is that of the ascending frontal parietal; the smaller superior posterior area that of the posterior parietal. The angular area is slightly inferior and posterior to this and the posterior temporal area is the basal triangle. The posterior temporal branches, however, also terminate in the inferior portion of the area assigned to the angular branch. The exact lines are not important; what is important is a mental picture of the areas outlined, and familiarity with the 4 branches on normal studies is indispensable to a recognition of the abnormal. Figures 1 and 2 are examples.

In Figure 1, there is occlusion of the as-

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From the Department of Radiology, University of Vermont College of Medicine, Burlington, Vermont.

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EMBOLIC OCCLUSIONS

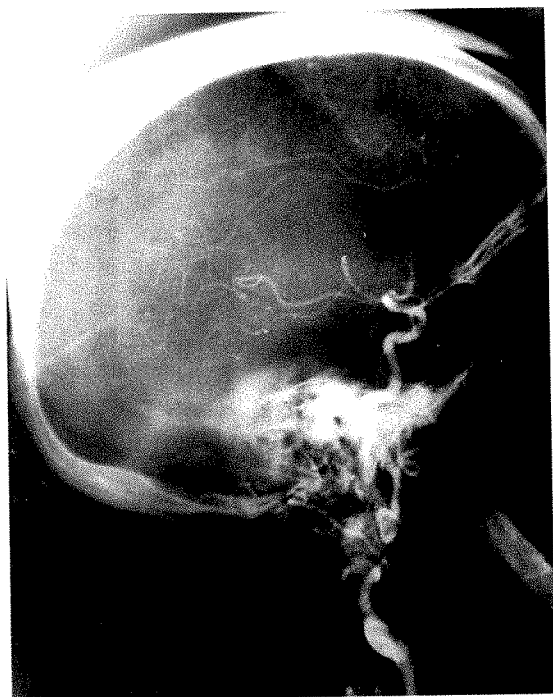


FIG. 1. A 69 year old man with right hemiparesis. There is complete absence of the ascending frontal branch.

ascending frontal parietal branch that is quite obvious. In Figure 2, however, the absence of the posterior temporal branch might be missed.

The angular branch, or a trunk supplying this area and that of the posterior parietal, is the best landmark for the axis of the sylvian group and, if missing, the diagram is difficult to complete. This itself is of diagnostic significance and emphasizes the point that the important element in recognizing branch occlusions is a concept of anatomy and not a few artificial lines. Figure 3 is an example.

The case demonstrated in Figure 1 showed evidence of collateral circulation to the involved area, but in our experience, contrary to that of Lanner and Rosengren,⁶ collateral circulation is not a reliable aid to the diagnosis of occlusion of the smaller vessels and is seldom prominent except when a larger trunk, such as the ascending frontal parietal or one that supplies two or more branches, is involved.

The first step in recognizing cerebral emboli is to think of them as a possibility. An embolus to the posterior fossa vessels as an isolated event was reported by Blume and Penzholtz.² Bladin,¹ in a roentgenologic and pathologic study of embolism of the internal carotid-middle cerebral artery axis, believed that a much larger proportion of strokes are caused by emboli in this region than currently realized, and Zatz and his colleagues²¹ reached the same conclusions in a study of intracerebral arterial occlusions.

The following conclusions are based on a study of 170 cases of angiographically proven occlusive cerebral vascular disease in which particular emphasis was given to occlusions of the small vessels. The term, "arteriosclerotic occlusion" as subsequently used is for convenience rather than exactness and implies the common vascular degenerative processes as opposed to embolization.

The location and presumed etiology of the small vessel occlusions are given in Tables I and II. There were 32 branch occlu-

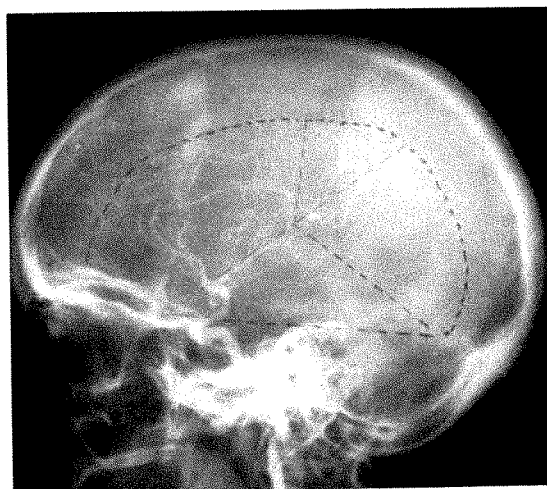


FIG. 2. A 31 year old woman with an acute stroke. The zones of termination of the 4 major divisions of the middle cerebral artery are shown in dotted lines. There is complete absence of the posterior temporal branch. This occlusion was considered probably embolic.



FIG. 3. A 55 year old woman with right hemiparesis. The zones of the 4 major branches of the middle cerebral artery are superimposed on the roentgenogram. The posterior parietal branch is unusually prominent; the posterior temporal branch leaves the sylvian fissure proximally and runs on the lateral aspect of the temporal lobe. The angular branch is absent. This occlusion was considered due to arteriosclerosis.

sions in 27 patients with only branches of the middle cerebral artery involved in 21. In 6 of the 27, the occlusions were considered definitely embolic and were probably embolic in 2 more. In 4 patients with more than 1 branch involved, the process was embolic in 3 and arteriosclerotic in 1. Of the 3 patients classified as "Other," 2 occlusions were associated with migraine and 1 oc-

	No. of Patients	Em-bolic	Arterio-sclerotic	Other
Isolated branch involved	23	5	15	3
More than one branch involved	4	3	1	
Generalized intracerebral embolization	4	4		

curred in childhood from unknown cause. In addition, 4 patients were seen with generalized intracerebral embolization who are not included in the 32 branch occlusions. There was good clinical correlation between occlusions and symptomatology in all cases except 1. This was an arteriosclerotic occlusion of the posterior cerebral artery found incidentally in a study showing a large frontal tumor.

Criteria for embolic versus arteriosclerotic occlusions were set up by applying findings in cases where the embolic process appeared obvious to other cases with occlusive disease. The diagnosis of arteriosclerotic occlusion was made by the presence of arteriosclerosis and the absence of changes expected in embolization, and, in cases where the point of obstruction was visible, by a typically tapered end to the vessel.

TABLE II
LOCATION AND ETIOLOGY OF SMALL VESSEL OCCLUSIONS IN 27 PATIENTS

Branch	No. of Patients	Embolic	Probably Embolic	Arterio-sclerotic	Other
Pericallosal	4	1		3	
Posterior Cerebral	5			4	1
Middle Cerebral					
Ascending Frontal Parietal	7	2		3	2
Posterior Temporal	9	2	2	5	
Angular	4	3		1	
Posterior Parietal	3	2		1	
Total	32	10	2	17	3

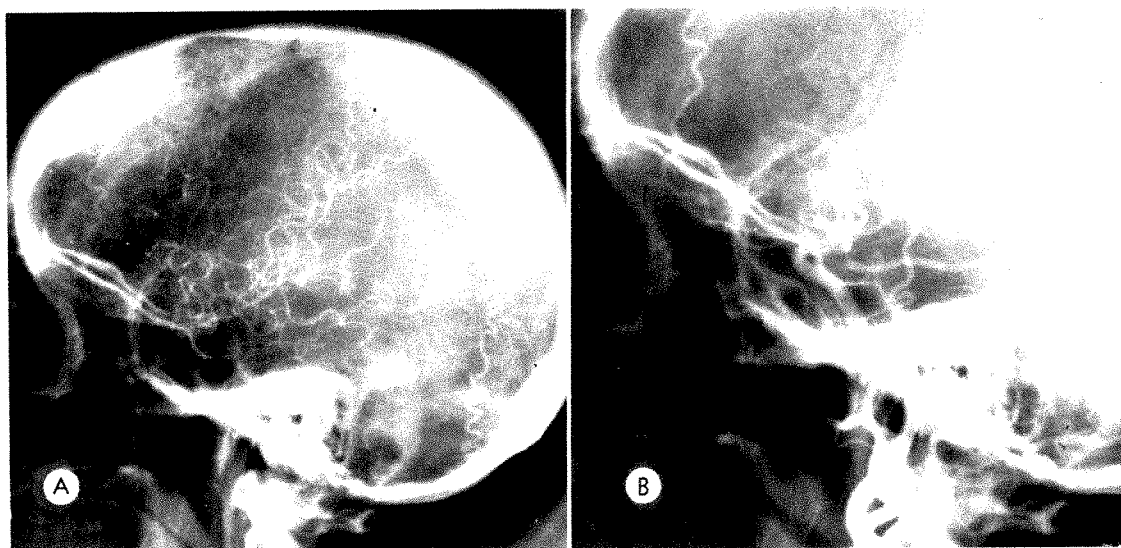


FIG. 4. (A) A 55 year old woman with a severe stroke and rapid deterioration. There is delayed circulation time as evidenced by the degree of filling of the external as opposed to the internal carotid branches, and lack of terminal arborization of the intracerebral vessel. The abrupt termination of one branch running to the angular area is typical of embolic occlusion. (B) An earlier roentgenogram of the same examination with slight enlargement. There is a filling defect in the supra-clonoid portion of the internal carotid artery, representing the thrombus responsible for the generalized embolization. The rounded filling defect in the posterior communicating artery probably represents an extension of the thrombus in the carotid.

Although the exact differentiation between a primary thrombosis or intimal fibrosis and embolus can only be made by the pathologist, there are angiographic differences that should, at least, suggest the likelihood of embolic occlusions:

1. Emboli are frequently multiple, especially to the smaller branches. This is not an absolute criterion as multiple branch occlusions occasionally occur in conjunction with generalized intracerebral arteriosclerosis and are seen with arteritis of the intracerebral vessels.

2. Embolic occlusions commonly occur in the absence of generalized intracerebral arteriosclerosis. It should be emphasized that, aside from the proximal trunks of the intracerebral vessels, arteriosclerosis, when present, tends to be generalized rather than spotty.²⁰ While the presence of generalized arteriosclerosis does not exclude embolism, its absence makes this diagnosis much more likely.

3. Occlusions of the smaller branches of the intracerebral vessels by arteriosclerosis

usually give a typically tapered end to the occlusions while embolic occlusions are usually abrupt. This point is not as helpful as it might appear as the actual point of obstruction, especially in the middle cerebral artery branches, is often concealed.

4. Emboli are not static as opposed to primary thromboses and may be seen to move as reported by Dalal *et al.*⁴ Emboli arising from the thrombus may disappear by lysis as demonstrated by Fischer and Adams⁵ in 1961. Emboli of atheromatous material, as recently described,^{17,18} cannot be expected to lyse, however, and primary thrombi have been reported to show recanalization by pathologists.¹⁹ Despite these limitations, we believe that disappearance of an occlusion is at least presumptive evidence of thrombotic embolus. One such case is included in this series.

5. Generalized embolization of the intracerebral vessels gives a characteristic picture with delayed circulation time, normal or dilated proximal branches and generalized

absence of terminal arterial arborization. This is such a distinct picture that there is no difficulty in recognizing it as such (see Fig. 4, *A* and *B*).

6. Although our series is too small for statistical validity, the patients with embolic occlusion seem to be appreciably younger than those with arteriosclerotic branch occlusions or primary thromboses of the carotid and main trunk of the middle cerebral artery.

CONCEALED EMBOLI

Emboli may be concealed by a proximal occlusion. Although the only cases we have seen with this condition involved the large, rather than small branches, we believe its importance warrants inclusion in this report. Since concealed large branch occlusions can be roentgenographically demonstrated, it is reasonable to suppose that smaller ones may be expected.

In the presence of a large mural thrombus at the carotid bifurcation, further reduction in blood flow past the narrowed segment due to embolization of a large intracerebral trunk may precipitate further thrombus development with complete occlusion. Two cases illustrating what we believe are steps of the evolution of this process are shown in Figures 5; and 6, *A* and *B*. In Figure 5, there is still sufficient patency of the carotid artery to show the occlusion of the middle cerebral artery with the exception of 1 small posterior temporal branch, and in Figure 6, *A* and *B* the carotid artery is completely occluded and the embolic occlusion of the middle cerebral artery only apparent from a study of the other side. Vertebral angiography was also done and likewise failed to show filling of the middle cerebral vessels. This finding is of clinical importance since the area involved in embolic occlusion is deprived of collateral circulation via the circle of Willis, and the presence or absence of intracerebral emboli may explain, in part, the marked variations in symptomatology in patients with unilateral carotid occlusion.

The intracerebral occlusions in the cases

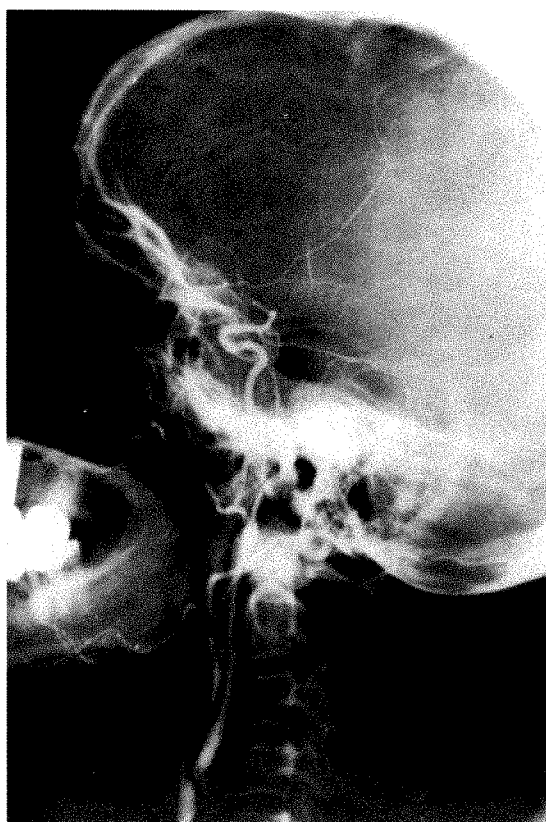


Fig. 5. A 41 year old woman with an acute stroke. There is almost complete occlusion of the internal carotid artery at its origin due to a soft thrombus that was surgically removed. Sufficient contrast material passes this point to opacify the internal carotid artery and there is faint filling of the pericallosal, posterior cerebral and anterior choroid arteries, but no filling of the middle group. The anteroposterior study verified this finding. The middle cerebral artery is occluded by an embolus arising from the thrombus in the carotid.

shown in Figures 5; and 6, *A* and *B*, were considered embolic rather than thrombotic for the following reasons: Both occurred in younger patients with normal cerebral arteries elsewhere who had good collateral circulation up to the point of occlusion; in 1 case a friable thrombus was surgically removed from the carotid artery, and in both cases the onset of symptoms was abrupt, suggesting an acute process rather than gradual stenosis with ischemia.

The source of emboli is often not obvious. Occasionally, there may be a known source

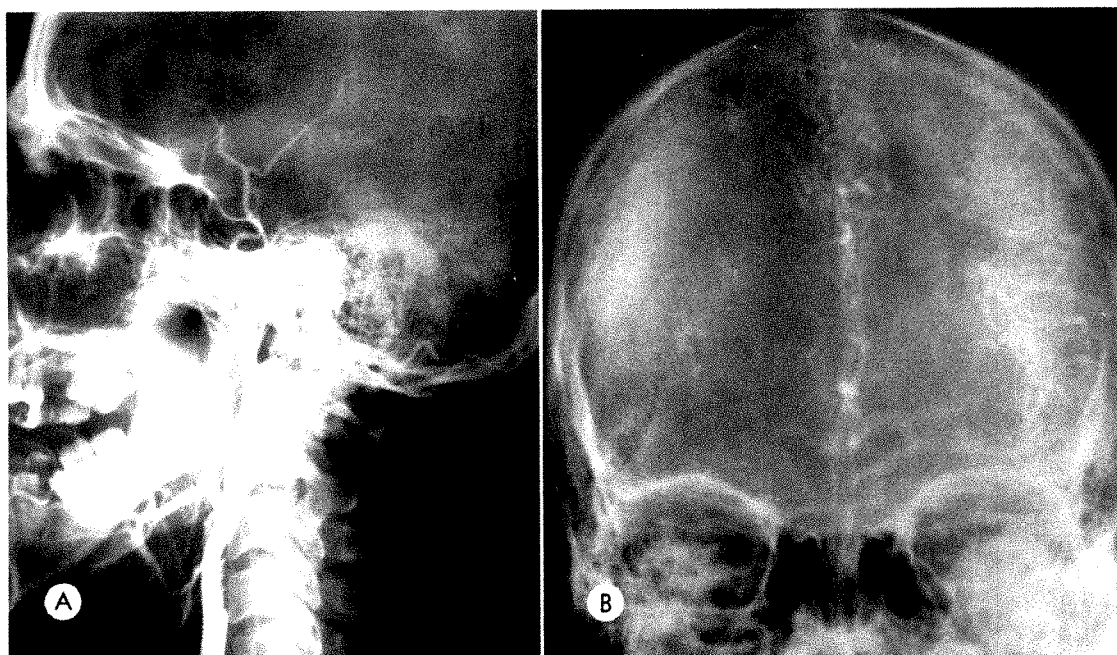


FIG. 6. (A) A 35 year old man with an acute stroke and a clinical course unusually severe for unilateral carotid artery occlusion. The internal carotid is completely occluded at its origin. (B) Carotid artery angiogram of the other side. Contrast material passes across the midline and a faint trace is seen running down the contralateral carotid artery to opacify the ophthalmic artery. The middle cerebral artery is occluded by an embolus arising from the thrombus in the carotid.

in the heart or aortic valve or the subclavian or innominate vessels in severe occlusive arteriosclerosis. It has been postulated that many arise from ulcerative lesions of the ascending aorta. That the carotid arteries themselves may be the source of emboli was suggested by Samuel¹⁵ in 1956, and since then has been noted by others.^{10,11} Schwartz and Mitchell¹⁶ found atheromatous ulcerations in the carotids, which may form the base for thrombi, in 11 per cent of male and 2.5 per cent of female cadavers. Richardson's group¹² suggested the carotids as sources of microemboli to the eye and brain. In this series of occlusions, the source of the embolus was known in 8 and could be seen in the carotid arteries in 4 (see Fig. 5; 6, A and B; and 7, A, B and C). In 3 of these the thrombus was at the site of the carotid bifurcation, but in 1 case (Fig. 4, A and B) a filling defect, considered to be a primary thrombus, could be seen in the intracranial portion of the carotid.

Although we agree with Lanner and Rosengren⁶ that intracerebral occlusions are easier to see with direct puncture of the internal carotid artery to avoid overlapping external branches, the significance of missing the source of emboli by this approach is so serious that we believe no cerebral angiography in the presence of vascular disease should be considered complete without a satisfactory look at the carotid artery from well below the bifurcation. The appearance of the friable thrombi located in the carotid sinus is a graphic reminder of Crawford's³ plea in 1956 that the carotid bifurcation be avoided in puncturing the vessel.

SUMMARY

A method of applying zones to the termination of the 4 major branches of the middle cerebral artery is described that has been very helpful in detecting occlusions of isolated branches of the intracerebral vessels. Many of these occlusions of small

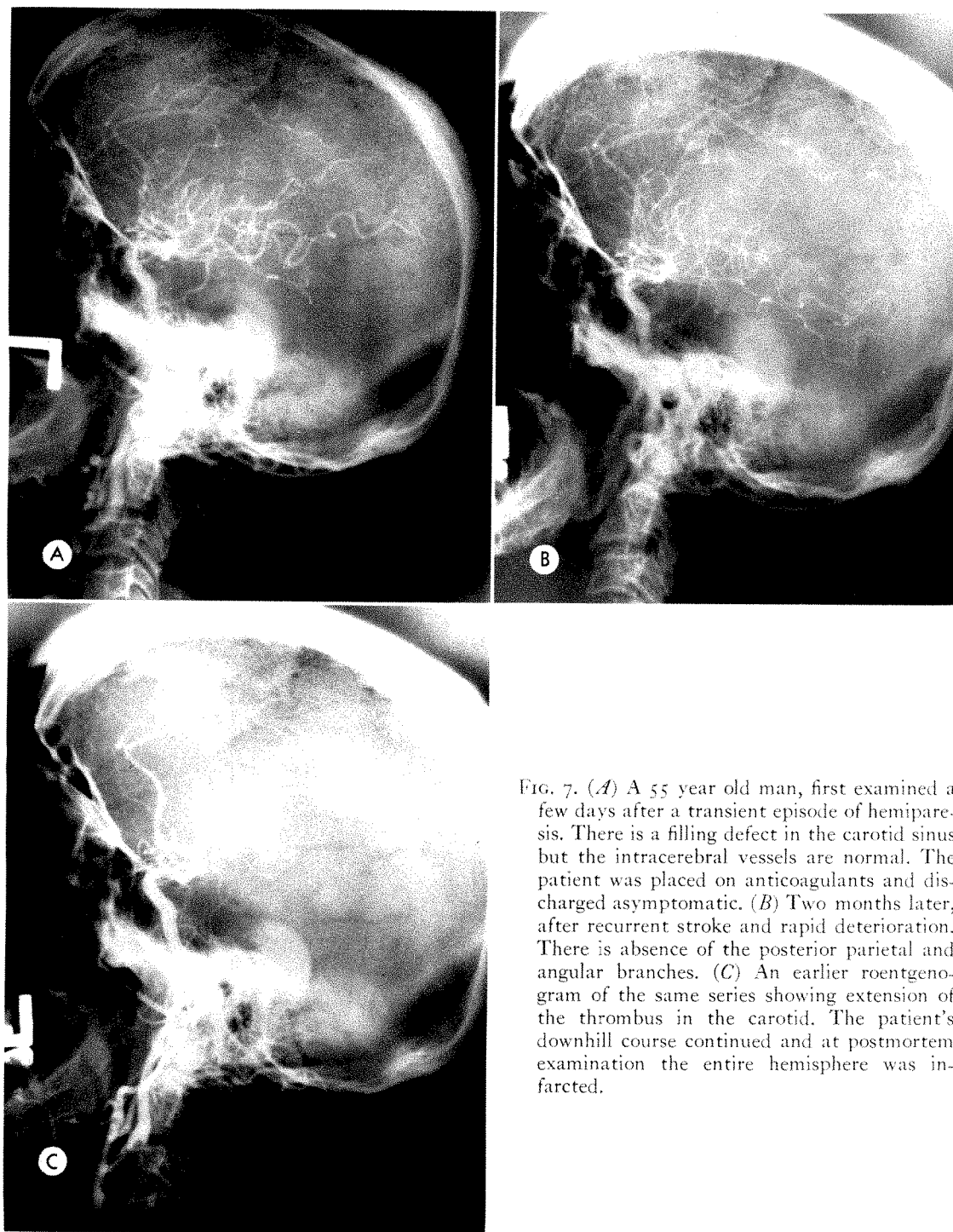


FIG. 7. (A) A 55 year old man, first examined a few days after a transient episode of hemiparesis. There is a filling defect in the carotid sinus but the intracerebral vessels are normal. The patient was placed on anticoagulants and discharged asymptomatic. (B) Two months later, after recurrent stroke and rapid deterioration. There is absence of the posterior parietal and angular branches. (C) An earlier roentgenogram of the same series showing extension of the thrombus in the carotid. The patient's downhill course continued and at postmortem examination the entire hemisphere was infarcted.

vessels are due to emboli and criteria for differentiation of embolic from other forms of occlusion are described.

Of all cases of angiographically proven occlusive cerebrovascular disease, small vessels were involved in about 15 per cent, and approximately one-third of these occlusions were due to emboli.

A thrombus responsible for the emboli was seen in the carotid artery in 4 cases.

Department of Radiology
University of Vermont
College of Medicine
Burlington, Vermont

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A COMPARATIVE STUDY OF VENTRICULOGRAPHY AND PNEUMOENCEPHALOGRAPHY FOR ROENTGENOGRAPHIC LANDMARKS DURING CRYOTHALAMECTOMY*

By JOSEPH M. WALTZ, M.D., and IRVING S. COOPER, M.D., PH.D.
NEW YORK, NEW YORK

THE purpose of this study is to compare the use of pneumoencephalography with ventriculography as a roentgenographic means of providing landmarks which serve to localize the intracerebral target within the thalamus during the operation of cryothalamectomy.¹ For 10 years, from 1953 to 1962, pneumoencephalography was employed routinely on our service for this purpose in a series of more than 2,000 cases.² Ventriculography was resorted to only when injection of air into the subarachnoid space failed to provide sufficient filling of the cerebral ventricles. The principal landmarks which are employed to localize the ventrolateral thalamic target during the course of our procedure, in addition to estimation of the size and shape of the ventricles, are the posterior border of the foramen of Monro and the center of the pineal gland. In those cases in which the pineal gland is not visualized, its position is ascertained by observing air in the cisterna of the greater vein of Galen and in the cisterna ambiens.

Because certain patients with far-advanced parkinsonism, particularly among the elderly, do not tolerate pneumoencephalography well, it was decided to substitute ventriculography in a series of cases, in order to compare various aspects of this procedure with pneumoencephalography for the purposes of cryogenic thalamic surgery.

METHOD

Pneumoencephalography was performed in the routine manner. Preparatory to being placed on the operating table, the patient

underwent a spinal tap between the fourth and fifth lumbar spine. A positive pressure was established with the injection, very slowly, of 35 to 45 cc. of air, followed by removal of approximately 25 cc. of cerebral spinal fluid. The patient was then placed on the operating table and fixed in the standard head holder for carrying out the basal ganglia surgery. Ventriculography was performed after the patient had been placed on the operating table with the head fixed in the head holder. A standard trephine was placed 4.5 cm. from the midline on the coronal suture, the dura was opened and the cortex bovied. The ventricular system was then tapped by means of a ventricular needle. Because of potential difficulty in obtaining adequate filling of the ventricular system, it was felt that a rigid cannula would be inadequate to completely fill the ventricular system at the level of the trephine. Therefore, a Scott flexible rubber cannula was used. It was directed in a medial posterior fashion using the contralateral infraorbital notch as the target. The cannula was passed through brain substance until the ventricular wall was perforated, then the stylet was removed and the cannula was threaded posteriorly, allowing its flexible tip to pass posterior to the trephine (Fig. 1). An air-fluid exchange was then carried out with approximately 5 cc. of positive air pressure being maintained, requiring approximately 25-35 cc. of air. In some cases it was impossible to direct the tip of the Scott cannula into the posterior part of the lateral ventricle (Fig. 2), but it was possible to completely fill the ventricular system by means of extracting all the

* From the Department of Neurologic Surgery, St. Barnabas Hospital, New York, New York. Supported in part by the John A. Hartford Foundation Inc., New York, New York.

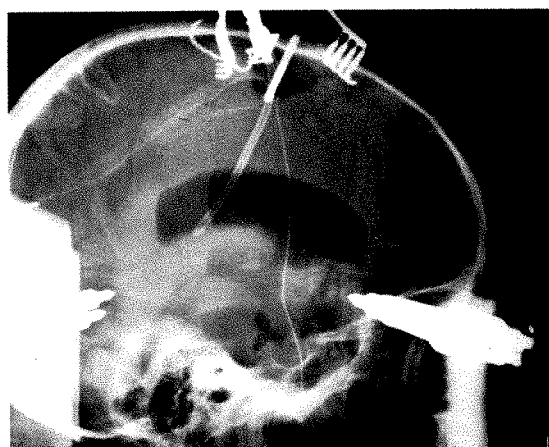


FIG. 1. Lateral roentgenogram obtained by ventriculography during the stereotactic placement of the cryogenic probe preparatory for making a cryosurgical lesion in the basal ganglia. Notice the position of the ventricular cannula in the posterior aspect of the lateral ventricular body with filling of the lateral ventricle, foramen of Monro, all of the third ventricle and the aqueduct of Sylvius.

fluid by gentle suction to a maximum of 50 cc. if indicated, and then injecting air until a slight pressure was felt on the syringe.

RESULTS

The groups were quite similar (Table 1), there being an equal distribution of the dyskinesias in both series consisting of Parkinson's disease, dystonia musculorum deformans, intention tremor, torticollis and choreo-athetosis. The mean age of the two groups was approximately the same—53 years (ventriculography 52.9 years; pneumoencephalography 53.8 years). They were also found to be equivalent in the mean number of days hospitalized, the ventriculography cases being hospitalized 13.4 and the pneumoencephalography patients 13.2 days. The number of cases entering the hospital for second side surgery was also similar with 26 per cent of the ventriculography and 23 per cent of the pneumoencephalography cases having second side cryothalamectomy.

It became rapidly apparent that the ventriculographic study showed the landmarks more clearly and allowed for better

TABLE I

TYPE OF DYSKINESIA CASES UNDERGOING
CRYOTHALAMECTOMY

	Ventriculography	Pneumoencephalography
Parkinson's Disease	88	90
Dystonia	3	8
Intention Tremor	4	0
Torticollis	2	1
Choreo-Athetosis	3	1
Total	100	100

target localization. Pneumoencephalographic studies (Fig. 3, *A* and *B*) in which frequently poor localization of the structures was noted were no longer obtained. Ventriculographic air studies with good localization (Fig. 1 and 2) were routine rather than the exception. For the purpose of comparison, an arbitrary criterion was established for rating the roentgenograms. Roentgenograms were rated 0 if no landmarks were identified, and 1 if only the foramen of Monro was visualized. Roentgenograms which showed the foramen of Monro, plus the pineal gland or suitable localization of the pineal gland, were given a rating of 2. A rating of 3 was given to roentgenograms which demonstrated, in

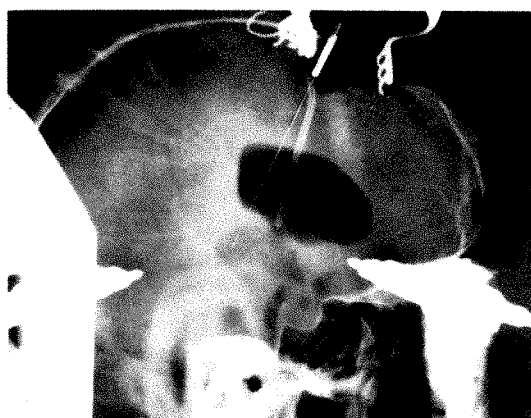


FIG. 2. Similar roentgenogram to Figure 1. Again ventriculography was employed for the visualization of the ventricular system. The anterior position of the Scott cannula is seen. Note complete filling of the ventricular system.

addition to the above, the anterior portion of the third ventricle. Roentgenograms demonstrating all of the third ventricle were rated 4, and 5 represented those roentgenograms which demonstrated all of the above landmarks plus the aqueduct of Sylvius. As noted in Table II, a large percentage of pneumoencephalograms showed inadequate visualization, with 31 per cent demonstrating only the foramen of Monro or less. In the ventriculographic study, only 1 per cent failed to demonstrate at least the pineal gland and foramen of Monro. A very large number (92 per cent) of the ventriculograms showed structures

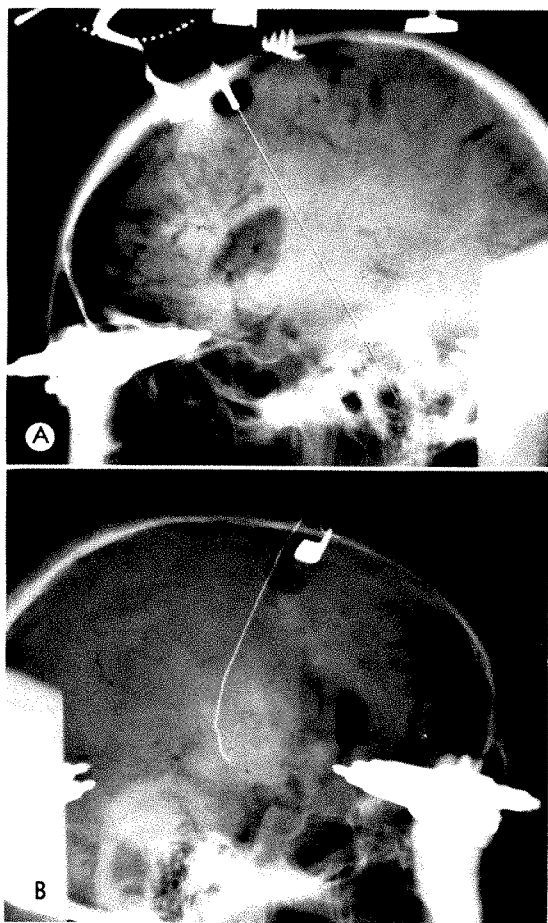


FIG. 3. (A and B) Lateral roentgenograms obtained using pneumoencephalography for localization of the target during cryothalamectomy. Notice the inadequate visualization of the structures necessary for adequate localization, *i.e.*, foramen of Monro and pineal gland.

TABLE II
RATING OF ROENTGENOGRAMS

Rating	Ventriculograms	Pneumoencephalograms
0	0%	7%
1	1%	24%
2	7%	32%
3	14%	16%
4	21%	13%
5	57%	7%
Mean Rating	4.2	2.2

over and above the basic landmarks of the foramen of Monro and pineal gland. The mean roentgenographic rating in the ventriculographic series was 4.2, which meant that all the foramen of Monro and pineal gland, all of the third ventricle and some of the aqueduct were demonstrated. In the case of the pneumoencephalogram, an average rating of 2.2 was obtained, meaning that slightly more than the foramen of Monro and pineal gland were demonstrated, which is just sufficient for localization of the target.

It was hoped that with better localization there would be less need to use multiple lesions to alleviate the patients' symptoms. However, very little difference was noted between the cases which had ventriculography and those with pneumoencephalography in this regard (Table III). It would appear from this comparison that better localization does not necessarily decrease the number of lesions needed. However, another aspect which should be considered is the possibility of a lesser recurrence rate

TABLE III
NUMBER OF CRYOGENIC LESIONS

	Ventriculography	Pneumoencephalography
1 Lesion	50%	52%
2 Lesions	42%	39%
3 Lesions	6%	9%
4 or More Lesions	2%	0%

TABLE IV
TOLERANCE TO AIR STUDY

	Ventricu- lography	Pneumo- encephalography
Good	98%	31%
Nausea and Vomiting	1%	15%
Headache	1%	45%
Changes in Sensorium	0%	24%

with more accurate lesion placement. A comparison of the recurrence rate between the pneumoencephalographic and the ventriculographic series showed that the recurrence rate was 12 per cent in the former and 9 per cent in the latter. Also noteworthy is the fact that in 59 per cent of the cases of recurrence in the pneumoencephalographic group, there were inadequate roentgenographic landmarks. Ventriculography with its better localization, therefore, may be assumed to lower the incidence of recurrence by 25 per cent.

The question originally proposed was not only one of improved roentgenographic localization, but also of the effect of the air study on the postoperative complications. The ventriculographic procedure was exceedingly well tolerated by 98 per cent of the patients in that group (Table IV) with only 1 per cent having some nausea and vomiting and 1 per cent having headache during the procedure. None of the patients showed any changes in sensorium. In the pneumoencephalographic series, however,

only 31 per cent of the patients tolerated the procedure well, with a 15 per cent incidence of nausea and vomiting and a 45 per cent incidence of headache. Twenty-four per cent of the patients showed transient changes in sensorium, *i.e.*, confusion or loss of consciousness.

A comparison of complications following the procedures (Table V) revealed rather interesting data. The incidence of headache in the pneumoencephalographic series was 10 times that of the ventriculographic group (52 per cent compared to 5 per cent). In the small number of cases having ventriculography which did suffer from headache, the symptoms disappeared by the end of the first day. In the pneumoencephalographic group, 87 per cent had symptoms which lasted longer than 3 days and in 17 per cent the headache persisted for longer than 1 week.

The incidence of nausea and vomiting was only 7 per cent in the patients having ventriculography and 26 per cent in those having pneumoencephalography. In 6 (86 per cent) of the 7 cases with nausea and vomiting in the ventriculographic group, the symptoms lasted only 1 day; in the remaining case, the symptoms lasted 3 days. Twenty-three patients (86 per cent) who had pneumoencephalography had nausea and vomiting lasting 3 days or more.

Mental confusion was noted in 17 per cent of the patients having ventriculography while in the pneumoencephalographic series 32 per cent of the cases

TABLE V
COMPLICATIONS

Days Present	Headache		Nausea and Vomiting		Confusion		Incontinence	
	Ventricu- lography	Pneumo- encephal- ography	Ventricu- lography	Pneumo- encephal- ography	Ventricu- lography	Pneumo- encephal- ography	Ventricu- lography	Pneumo- encephal- ography
None	95%	48%	93%	74%	83%	68%	88%	81%
3 days	5%	20%	7%	17%	5%	3%	1%	1%
3-7 days	0%	23%	0%	7%	5%	11%	2%	5%
Over 7 days	0%	9%	0%	2%	7%	18%	9%	13%

showed mental confusion, almost twice the incidence of those in the ventriculographic group. Some mental confusion which lasted 7 or more days was noted in 12 patients having ventriculography compared with 29 cases with pneumoencephalography.

Urinary incontinence was observed in the ventriculographic study in 12 per cent of cases, while in the pneumoencephalographic series 19 per cent showed urinary incontinence. Urinary incontinence is a transient complication following thalamic surgery which lasts approximately 10 days to 2 weeks in the most severe cases.

Balance difficulty was noted in 33 per cent of the patients with ventriculography and in 34 per cent of those with pneumoencephalography. This is a complication resulting from the temporary interruption of extrapyramidal pathways which requires reorientation of the nervous system and is completely responsive to physical therapy and time. In almost all cases this complication had disappeared within a week to 2 weeks. Major complications were noted to be quite similar in that the mortality rate in each series was 1 per cent, usually secondary to operative hemorrhage. Hemiplegia was noted in 2 per cent of the cases in each series with all cases showing improvement with physical therapy and time.

DISCUSSION

On the basis of a comparison of 100 consecutive cases of cryothalamectomy using ventriculography and an equal number in which pneumoencephalography was employed, it may be concluded that ventriculography is more easily tolerated, the patient evidencing less nausea, vomiting and headache, and having no problem with sensorium changes. A lesser incidence of postoperative complication of headache,

nausea and vomiting, and mental confusion was noted in the ventriculographic series. There was little or no effect of ventriculography on the incidence of incontinence, length of hospitalization, or major complications. Also, better visualization of the structures essential to roentgenographic localization of the target area was obtained on the ventriculograms. No differences were noted in the number of lesions needed for the clinical alleviation of the patients' symptoms; however, there was a decrease in the rate of recurrence of symptoms in the ventriculographic group.

SUMMARY

A study comparing pneumoencephalography and ventriculography in patients undergoing basal ganglia surgery is presented. In each series 100 cases were used and compared as to target localization, tolerance of the patient to the air study and postoperative complications. It was found that ventriculography was better tolerated by the patient and that the patient had fewer postoperative problems, *i.e.*, headache, nausea, vomiting and mental confusion. Ventriculography also gave better visualization of intracerebral landmarks and was considered preferable to pneumoencephalography in the localization of the cerebral target prior to cryothalamectomy.

Joseph M. Waltz, M.D.
Department of Neurologic Surgery
St. Barnabas Hospital
4422 Third Avenue
New York, New York 10457

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TOMOGRAPHY IN CHOLESTEATOMA OF THE TEMPORAL BONE*

CORRELATION BETWEEN THE STANDARD ROENTGENOGRAPHIC EXAMINATIONS AND TOMOGRAPHY

By S. BRÜNNER, M.D., O. PETERSEN, M.D., and L. E. SANDBERG, M.D.

GENTOFTE, DENMARK

THE current clinical otologic methods, primarily otoscopy and irrigation of the cupular space, sometimes fail in the diagnosis of cholesteatoma. Therefore, a search has been made for more reliable methods, and in this field roentgenographic examination of the temporal bone in various projections has proved of considerable value.

It is important to diagnose a cholesteatoma at an early stage, before it has caused irreparable changes in the temporal bone. It is in these cases that roentgenographic studies may be of great value. However, studies in the conventional projections appear to have reached the limit of their capacity, and, as is evident from the reports of MacMillan⁸ and Winderen and Zimmer,¹⁰ preoperative confirmation cannot be obtained in more than 60 to 70 per cent of the cases. Tomography, especially with the use of multidirectional blurring, for example with the polytome (Massiot), has proved most promising. In 1959 Tarp⁹ published the tomographic results in patients with cholesteatoma. In 19 out of 22 surgically verified cases, he had demonstrated cavity formation by tomography. This material is included in our present study. In 1960 Brünner, Jensen and Jespersen² in 21 operative verified cases found cholesteatomas in 17 instances (81 per cent) by using linear tomography.

MATERIAL

For the purpose of assessing the capability of tomography in the early stages of cholesteatoma, we have analyzed, in the Gentofte Hospital, Copenhagen, a series of 98 cases of surgically verified cholestea-

tomas, all of which had been examined preoperatively by multidirectional tomography (using Massiot's polytome). The series comprised 57 males and 41 females. Twenty-five were children under 15 years of age, including 12 below 10 and 4 below 5 years of age. At the other extreme, 4 patients over 70 years of age were subjected to operation (Table I).

The clinical preoperative diagnosis is shown in Table II. In 61 cases (62 per cent) a diagnosis of cholesteatoma had been made. In 59 patients cholesteatoma masses had been seen, while in 2 cases the lesion was suspected because cholesteatoma scales were found on irrigation and marginal perforation was present. Contrariwise, there was no clinical suspicion of cholesteatoma in 37 cases (38 per cent), in which the operative indication had to be based upon the roentgenologic investigation.

The site and size of the cholesteatomas as indicated by the operative records, are shown in Table III. Large cholesteatomas are those masses which exceed bean size,

TABLE I
AGE DISTRIBUTION (AT OPERATION)

Age (yr.)	0-5	6-15	16-30	31-70	over 70
No.	4	21	23	46	4

TABLE II
CLINICAL PREOPERATIVE DIAGNOSIS

Definite Cholesteatoma	59 cases (60%)
Suspicion of Cholesteatoma	2 cases (2%)
No Cholesteatoma	37 cases (38%)

* From the Department of Radiology and the Department of Otology, Gentofte Hospital, Copenhagen, Denmark.

TABLE III
SITE AND SIZE OF CHOLESTEATOMA (AT OPERATION)

Site	No. of Cases	Large	Small	Not Stated
Antrum	25	14	3	8
Antrum and Attic	58	31	8	19
Attic	15	9	4	2
Total	98	54	15	29

small cholesteatomas below that size. As is apparent from the table, the material consisted mainly of fairly large cholesteatomas. Fifty-four are categorized as large and only 15 as small. In 29 cases there was no information concerning size. It may also be seen that the great majority of cholesteatomas was situated both in the antrum and attic and in 25 cases in the antrum only. As far as the site is concerned, a distinction is made only between lesions of the antrum and the attic, since the aditus may be defined as the anatomic border between the antrum and the attic.

ROENTGEN FINDINGS

In all patients preoperative tomography in the anteroposterior projection had been performed. Lateral tomography was performed in only a few cases since the anteroposterior study generally gives sufficient information about the appearance of lesions in the attic and antrum.³ Only in cases where the cholesteatomas were complicated by facial palsy was lateral tomography necessary in order to visualize in detail the course of the facial canal.⁴ Prior to tomography, all patients had conventional roentgenography in 4 projections, *i.e.*, *Stenvers'*, *Schüller's*, *Towne's* and *transorbital* views. These views could be compared with the tomographic studies in only 67 cases, because the conventional roentgenograms for the remaining patients could not be obtained. In these cases, the findings were compared with those on the reports given by other radiologists.

A special problem was posed by the to-

mographic exposures in children.¹⁻⁶ As cuts of 1 mm. require an absolutely quiet patient, anaesthetic assistance was sought in these cases. The infants under 1 year of age received a so-called "lytic cocktail," which contains per milliliter, 28 mg. pethidine, 7 mg. chlorpromazine and 7 mg. promethazine. The dosage was 0.05 mg./kg. body weight. Children over 1 year of age were given pentothal sodium rectally. Empirically, children over 6 or 7 years of age do not need drugs to keep them quiet.⁵

Table IV shows that roentgenologically there was evidence or suspicion of cholesteatoma in 94 per cent of the cases. This value was found in retrospect, by a review of the roentgenograms, while the preoperative roentgenographic reports indicated a somewhat lower value (71 per cent) due to various viewer routines in reading the tomographic films. A comparison of the capability of the various standard roentgenographic projections and tomography to demonstrate the cholesteatoma, in the 67 cases where a comparison was possible (Table V), showed clearly the superiority of tomography. By combining the standard projections, the cholesteatomas were found in only 58 per cent of the patients, but with tomography they were demonstrated in 92 per cent. It may also be seen from Table VI that in a comparison of various series using varied projections, tomography proved superior to the other methods in diagnosing cholesteatoma. This is because tomography is more adequate in demonstrating the antrum and attic and their bony walls. The difficulty encountered in the other projections is the unavoidable superimposition of these regions.

The size as well as the site influences the diagnosis of cholesteatoma (Table VII). In

TABLE IV
TOMOGRAPHIC DIAGNOSIS IN 98 CASES

Cholesteatoma	54 cases	} 94%
Suspicion of Cholesteatoma	38 cases	
No Cholesteatoma	6 cases	6%

TABLE V
COMPARISON OF TOMOGRAPHY AND STANDARD ROENTGENOGRAPHIC PROCEDURES IN 67 CASES

	Schüller	Stenvers	Trans-orbital	Towne	Stenvers, Trans-orbital and Towne	Schüller, Stenvers, Towne and Transorbital	Tomography
Cholesteatoma or Suspicion of Cholesteatoma	21=31%	10=15%	24=36%	28=42%	35=52%	39=58%	62=92%

TABLE VI
ASSESSMENT OF VARIOUS PROJECTIONS IN A NUMBER OF REPORTED SERIES

Authors	No. of Cholesteatomas	Projections						Combination of Various Projections	Tomography
		Law	Towne	Trans-orbital	Schüller	Runström	Chaussé III		
MacMillan, ¹ 1936	288	45%	68%						
Winderen and Zimmer, ¹⁰ 1954	131							87%	
Chiat and Kittredge, ⁷ 1958	25								50%
Tarp, ¹ 1959	22								86%
Brünner, Jensen and Jespersen, ² 1960	80				40%	26%	62%		
Brünner, Jensen and Jespersen, ² 1960	(21)				(47%)	(33%)	(71%)		(81%)
Brünner, Petersen and Sandberg, 1966	98								94%
Brünner, Petersen and Sandberg, 1966	(67)		(42%)	(36%)	(31%)			(58%)	(92%)

TABLE VII
CORRELATION BETWEEN THE SIZE OF CHOLESTEATOMA AND TOMOGRAPHIC DIAGNOSIS

Size of Cholesteatoma at Operation		Tomographic Diagnosis			
		Definite Cholesteatoma	Suspicion of Cholesteatoma	Cholesteatoma and Suspicion of Cholesteatoma	Incorrect Diagnosis
Large	54	38	15	53	1
Small	15	4	9	13	2
Not stated	29	12	14	26	3
Total	98	54	38	92	6

38 (70 per cent) of the 54 cases definitely showing cholesteatoma by tomography, the lesions were considered large.

Roentgen measurement of the antral cavity in 66 cases showed it to exceed 6 mm. in width and 10 mm. in height, which is

considered as the upper limit of normal.⁸

The site of the cholesteatoma is also of great importance in the roentgenographic diagnosis and, of course, in planning the operation. Out of the 25 cases in which the cholesteatomas were situated only in the

TABLE VIII
CORRELATION OF SITE AND TOMOGRAPHIC DIAGNOSIS

	Antrum	Antrum and Attic	Attic
Cholesteatoma or Suspicion of Cholesteatoma	22	56	14
No Cholesteatoma	3	2	1
Total	25	58	15

antrum, the diagnosis was correct in 22 (Table VIII). The 3 remaining cases included 2 secondary cholesteatomas in previous cavities left by radical mastoidectomy. Out of the 15 cases in which the cholesteatoma was situated exclusively in the attic, a tomographic diagnosis of cholesteatoma was made in 14. The only case in which tomography failed to demonstrate the lesion was found, at operation, to be a small cholesteatoma in the attic. Out of the 58 cases in which the cholesteatomas in-

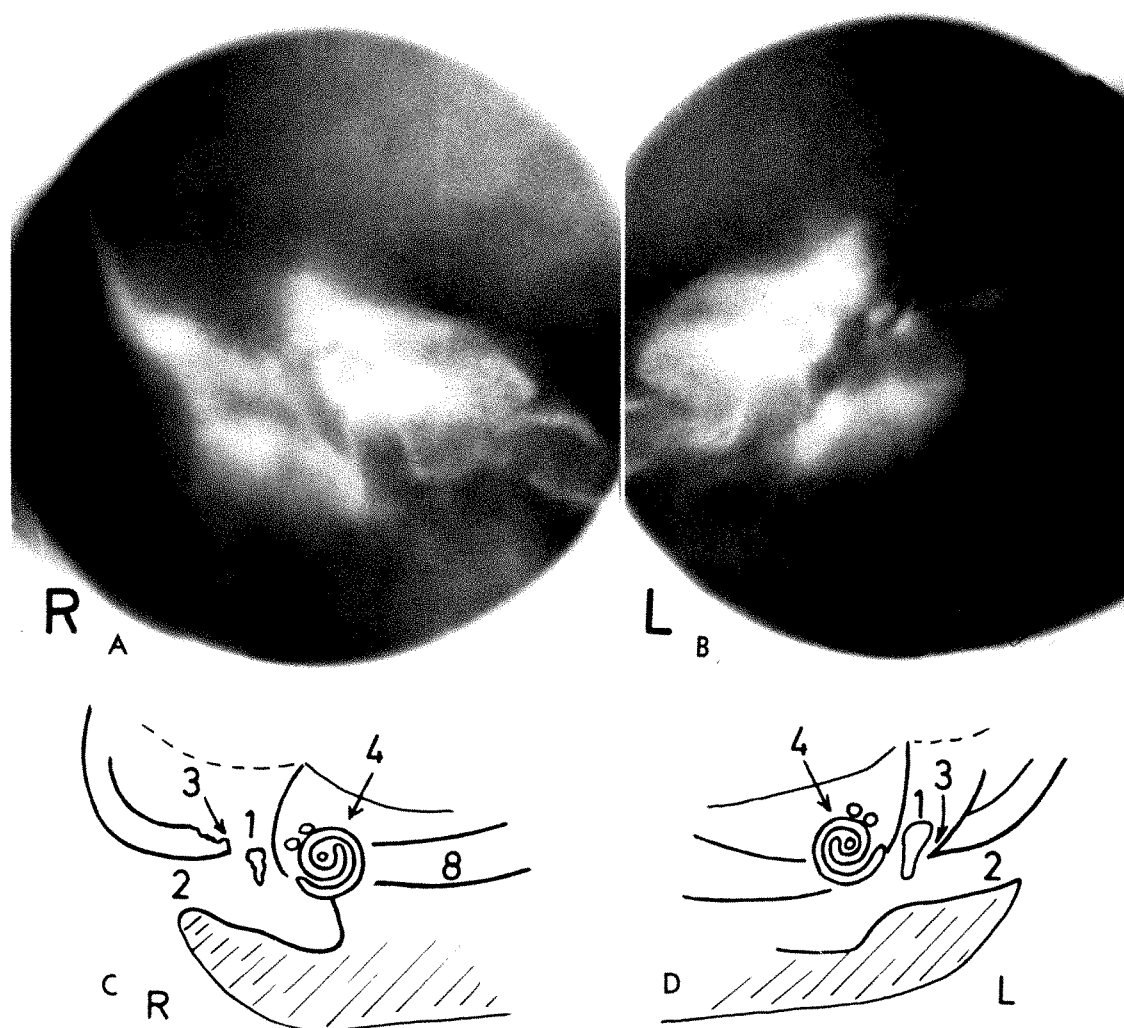


FIG. 1. Twenty-one year old woman with cholesteatoma in the *right* attic. (A) Anteroposterior tomogram in the cochlea plane showing destruction of the spur and the lateral wall of the attic and fragmentation of the ossicles. (B) Normal left side for comparison. (C and D) Diagrams of A and B, respectively: (1) ossicles; (2) external auditory meatus; (3) spur; (4) cochlea; and (8) internal auditory meatus.

volved the antrum as well as the attic, a correct diagnosis was made in 56. The remaining 2 were secondary cholesteatomas in old operation cavities.

Cholesteatomas in the attic are often difficult to differentiate from chronic otitis, since the changes are similar, *i.e.*, destruction and decalcification; however, often no definite cavity formation is present in otitis. In our experience, an important diagnostic sign in cholesteatomas has been destruction of the tip of the spur and of the

lateral attic wall. Figures 1*A* and 2*B* show typical attic cholesteatomas with destruction of the tip of the spur and the lateral attic wall. When these changes are present, cholesteatoma should be considered, although similar changes may be seen in a few cases of chronic otitis.

In 27 cases of cholesteatomas, localized either to the attic or to the attic and antrum, the operative records contained information pertaining to destructive lesions of the tip of the spur. In 25 of these cases

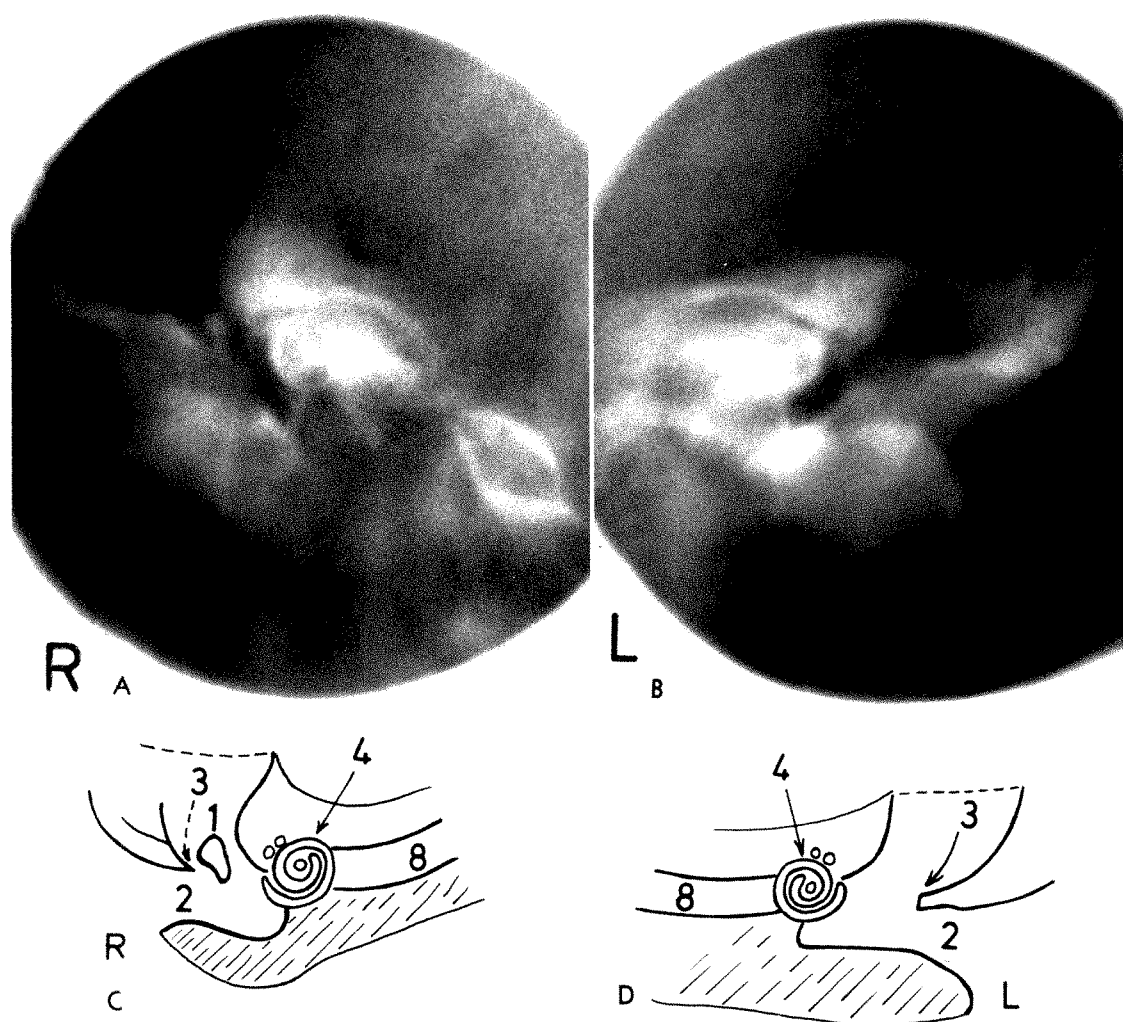


FIG. 2. Sixty-two year old woman with cholesteatoma in the *left* attic and antrum. (*B*) Anteroposterior tomogram in the cochlea plane showing destruction of the ossicles, spur and the lateral wall of the attic on the left side. (*A*) Normal right side for comparison. (*C* and *D*) Diagrams of *A* and *B*, respectively: (1) ossicles; (2) external auditory meatus; (3) spur; (4) cochlea; and (8) internal auditory meatus.

(92 per cent) tomography showed abnormal changes of the spur tips and the lateral attic walls.

Cholesteatomas of the antrum are characterized by cavity formation. These cavities are usually smooth-walled and show marginal sclerosis (Fig. 3*B* and 4*B*). This was noted in 58 out of the 74 cases of cholesteatomas (78 per cent) localized to the antral region.

DISCUSSION

Out of the 61 cases in which, clinically, cholesteatoma was diagnosed or strongly suspected, tomography showed definite evidence or suspicion in 59 (Table 1x). It may be said, that it did not provide a definitive diagnosis, but it did support the clinical diagnosis, and gave valuable supplementary information regarding the localization, size and possible destructive

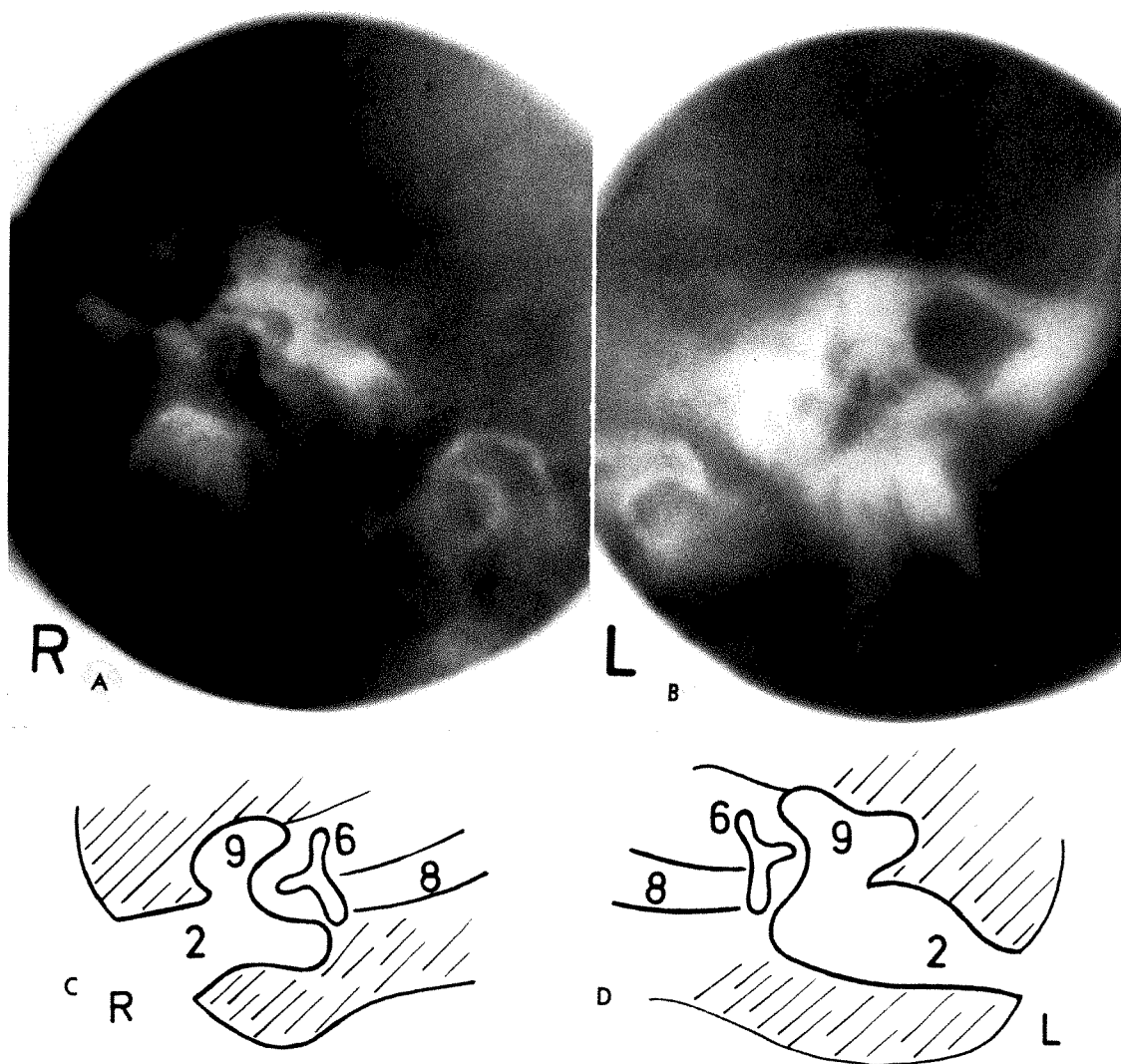


FIG. 3. Same patient as in Figure 2. (B) Tomogram 2 mm. more posteriorly in the semicircular plane showing a large cholesteatoma cavity in the *left* antrum. (A) Normal right side for comparison. (C and D) Diagrams of A and B, respectively: (2) external auditory meatus; (6) semicircular canals; (8) internal auditory meatus; and (9) antrum.

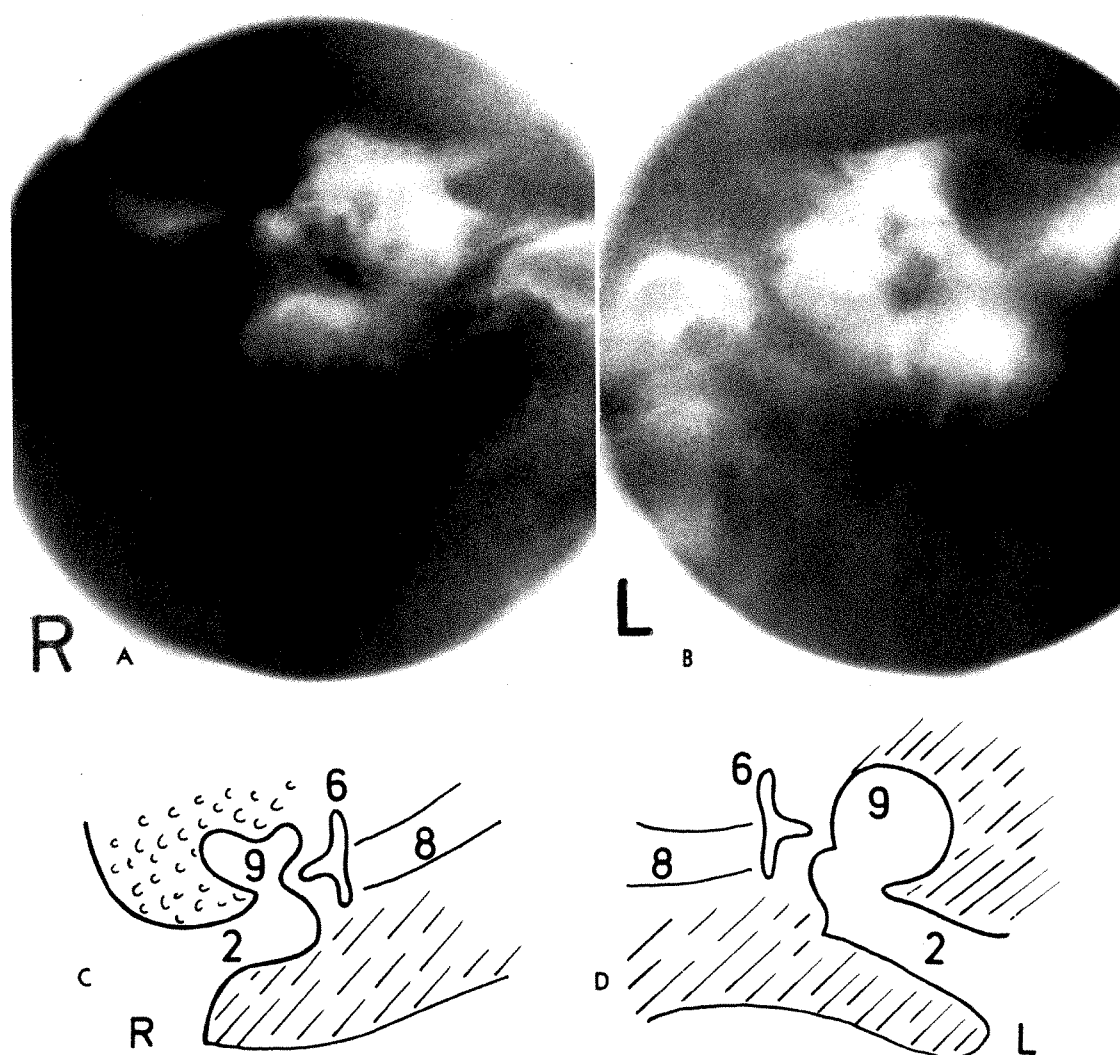


FIG. 4. Twenty-nine year old man with cholesteatoma in the *left* antrum. (B) Anteroposterior tomogram in the semicircular plane showing a large cholesteatoma cavity in the left antrum. (A) Normal right side for comparison. (C and D) Diagrams of A and B; respectively: (2) external auditory meatus; (6) semicircular canals; (8) internal auditory meatus; and (9) antrum.

TABLE IX

CORRELATION BETWEEN THE CLINICAL AND TOMOGRAPHIC DIAGNOSIS OF CHOLESTEATOMA

Clinical Diagnosis	Tomographic Diagnosis			
	Definite	Possible	Total of Definite and Possible Cases	Incorrect Diagnosis
Certain: 61 cases (62%)	35	24	59 (97%)	2 (3%)
No Cholesteatoma: 37 cases (38%)	19	14	33 (89%)	4 (11%)
Total: 98	54	38	92 (94%)	6 (6%)

changes. In 37 cases in which the otologists could *not* make a clinical diagnosis of cholesteatoma but only a diagnosis of chronic otitis, tomography revealed the definite diagnosis in 19 (about 50 per cent) and a suspicion in another 14. In other words, tomography proved to be of diagnostic value in 89 per cent of these cases.

It is important to differentiate a cholesteatoma cavity from a normal mastoid antrum. With large cholesteatomas in the antral region, the outline of the antrum is frequently very distinct and thus its size can easily be measured. MacMillan⁸ stated that the mastoid antrum measures 6 mm. in the transverse and 10 mm. in the vertical diameter in anteroposterior projection. Tarp⁹ feels that it is smaller measuring 8 mm. in transverse and 6 mm. in the vertical diameter. The antrum is sometimes enlarged, but this can be a normal anatomic variation which is always bilateral. Simultaneous tomography of both ears should, therefore, be performed. In the present series, 66 cases showed a roentgenologically large antrum measuring more than 6 mm. in the transverse and 11 mm. in the vertical diameter.

Cholesteatomas confined to the attic are more difficult to diagnose since they do not produce a cavity; however, destruction of the spur and the lateral attic wall, ossicles and, in some cases, the cochlea and semicircular canals may be noted. Roentgenologically, this may resemble chronic otitis, but, in a material of 60 cases of simple chronic otitis operatively verified in our department, only 2 cases (3 per cent) showed destruction of the spur and the lateral attic wall in the tomograms. It may be assumed, therefore, that this finding indicates a high probability of a cholesteatoma in the attic. In cases where cholesteatomas were localized in the region of the attic there was destruction of the spur and the lateral attic wall in approximately 92 per cent.

In patients who previously had had a mastoid operation, it is often impossible to visualize cholesteatomas in the operative cavity, and in these cases, tomography is not of diagnostic value.

CONCLUSION

1. Tomography has proved to be the method of choice in the preoperative roentgen diagnosis of cholesteatoma; it is recommended also in all cases of chronic otitis.

2. A smooth-walled, enlarged antral cavity is an important diagnostic finding in cases of cholesteatoma in the antrum. Both ears should be tomographed for comparison.

3. Destruction of the spur and the lateral wall of the attic usually indicates a cholesteatoma in the attic.

4. In cases of previous radical mastoidectomy, roentgenographic studies, including tomography, are of little value since cholesteatomas are difficult to define in the operative cavity.

SUMMARY

The roentgenographic findings in the attic and antrum in 98 cases of surgically confirmed cholesteatoma are discussed. Tomography was found to be the best method of demonstrating this lesion.

Cholesteatomas were correctly diagnosed or suspected in 94 per cent of the cases in the present series.

It is recommended that tomography be used in all cases of chronic otitis, where there is a clinical suspicion of cholesteatoma.

S. Brünner, M.D.
Department of Radiology
Gentofte Hospital
Copenhagen, Denmark

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JUGULAR FORAMEN AND EARLY ROENTGEN DIAGNOSIS OF GLOMUS JUGULARE TUMOR

By SEUK KY KIM, M.D.,* and M. PAUL CAPP, M.D.†
DURHAM, NORTH CAROLINA

THE pertinent roentgen features of glomus jugulare tumor⁶ include the specific finding of bone destruction at the medial portion of the petrous pyramid and the nonspecific changes of opacification and sclerosis of the mastoid due to extension of the tumor. Generally, these roentgenographic changes are evident only when the disease has advanced. The purpose of the authors is to describe a new technique which is capable of detecting earlier roentgen changes than those seen using conventional methods.

The jugular foramen is bounded by the temporal and occipital bones. It is an aperture between the medial and lateral portions of the occipito-temporal suture. The temporal side of the foramen is the jugular fossa (bulb), bounded superiorly by the bony floor of the middle ear. The glomus jugulare lies in the fossa or middle ear near the fossa,^{4,5} and the glomus tumor arises in this area.^{1,6} Erosion of the fossa is an early manifestation of this tumor, and it is at this stage of the disease that a new technique would be valuable. The size of the foramen varies² greatly, and small asymmetric variations in size are usually of no diagnostic value. In fact, the right-sided foramen is usually larger than the left. Evaluation of the bony cortex of the foramen, especially at the jugular fossa, is, therefore, most important.

The jugular foramen is an oblique canal at the base of the skull; therefore, difficult to demonstrate roentgenographically. The modified submentovertex view³ often fails to satisfactorily demonstrate the jugular foramen due to overlying structures of the temporal bone and atlas. In addition, the end of the sigmoid sinus may lead to the

false impression of enlargement of the foramen. We have found that the foramen is best demonstrated by a modified open-mouth Waters' sinus view.

TECHNIQUE

In Figure 1, a modified Waters' view, the position of the skull is shown. The mouth is opened as wide as possible. The cantho-meatal line and roentgenographic table form a 37° angle. This angle may vary from 35° to 37° in different patients, due to anatomic bone variations. The roentgen-ray beam is directed perpendicular to the table at the level of the external auditory meatus. A small cone to include both jugular foramina is used for better detail. We use a 3 × 5 cm. lead cut-out field attached to the

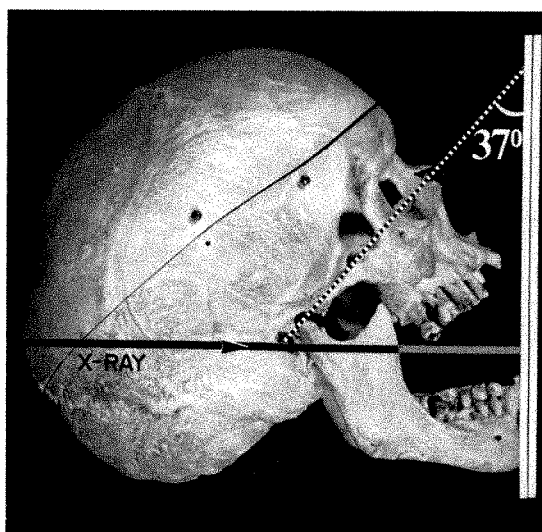


FIG. 1. Position of modified open-mouth Waters' view. Cantho-meatal line forms a 37° angle with the table. The roentgen-ray beam is directed perpendicular to the table at the level of the external auditory meatus.

* Assistant Professor in Radiology, Duke University Medical Center; Acting Chief, Radiology Service, VA Hospital, Durham, North Carolina.

† Assistant Professor in Radiology, Duke University Medical Center, Durham, North Carolina.

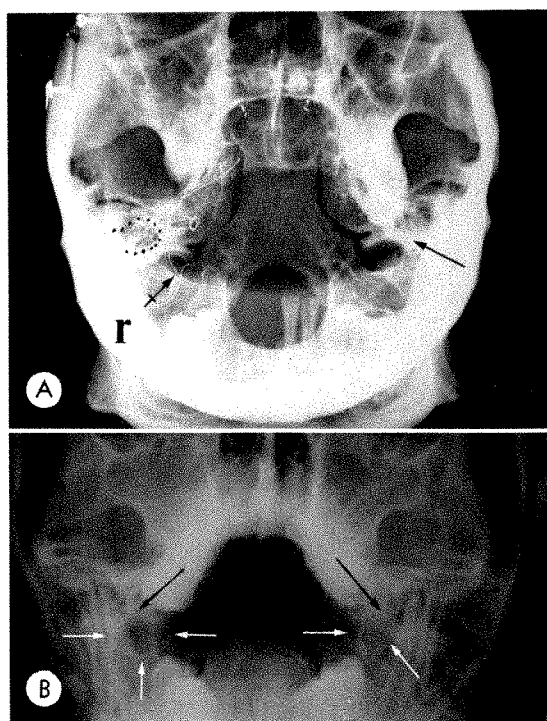


FIG. 2. (A) The modified Waters' view of the dry skull. The white "C"-shaped wire mark (↔) is the right-sided jugular foramen. The dotted line outlines the middle ear cavity and part of the external auditory meatus. The parallel white lines medial to the crossed arrow outline the sigmoid sinus. On the left side, the arrow points to the bony septum (middle ear floor) between the jugular fossa and middle ear cavity. (B) The modified Waters' view of a normal case. The white arrows point to the jugular foramen which is projected between the upper and lower molar teeth and medial to each ramus of the mandible. The black arrows point to the bony septum between the jugular fossa and the middle ear cavity.

Franklin head unit. Either the postero-anterior or anteroposterior position can be used but the former is easier. In case of an inadequate open-mouth study, a few degrees' side tilt of the face is necessary to project one foramen under the palate and the other foramen in between the teeth and ramus of the mandible.

Figure 2A is a modified open-mouth Waters' view showing the jugular foramen and its bony cortex in a dry skull. Figure 2B is the same view of a normal case. The bony floor between the middle ear cavity and the jugular fossa is also well seen.

Another valuable view to detect erosion of the jugular fossa is the modified Law's mastoid view. In Figure 3, a modified Law's view, the position of the skull is shown. The left side of the face is against the roentgenographic table when the left jugular foramen is examined. The procedure is as follows: (a) the face is tilted to the side, toward the table, to make a 5° angle between the sagittal suture line and table; (b) the chin is tilted toward the table to make a 15° angle between the nasal axis line and the table; and (c) the roentgen-ray tube is tilted 15° caudad and the central beam is directed to the external auditory meatus of the ear to be examined.

In Figure 4 are examples of a modified Law's view. "S" is a dry human skull which shows the right jugular foramen clearly (X). The dense area (white arrow on "S") between the foramen and auditory meatus (dotted oval), anterior to the mastoid process, is due to the surrounding bones of the jugular fossa, including the floor of the middle ear. The crossed arrow on "S" points to the end of the sigmoid sinus. These details are not as well recognized on the hu-

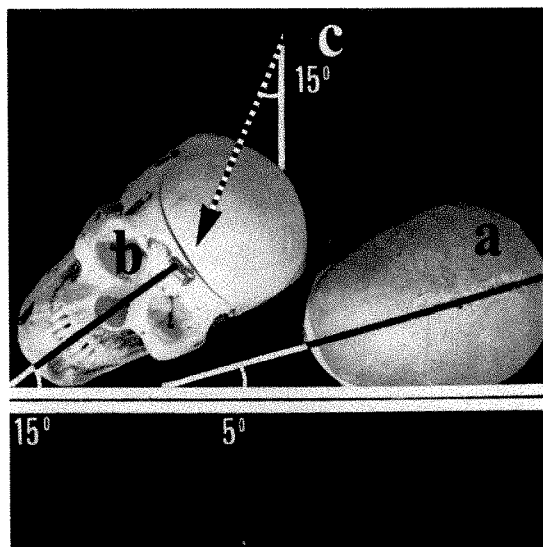


FIG. 3. Positions of modified Law's view. (a) The sagittal suture line and table form a 5° angle. (b) The nasal axis line and table form a 15° angle. (c) Fifteen degree caudad tilt of the roentgen-ray tube.



FIG. 4. Modified Law's view of dry skull (S) and Case 1 (R and L). On S, "X" lies in the jugular foramen. The dotted oval outlines the external auditory meatus. (→) points to the dense bony area between the jugular foramen, auditory meatus, and anterior part of the mastoid process. (↔) is the distal sigmoid sinus. "L" is the normal left mastoid of Case 1 showing (→) bony density below the meatus. "R" is the abnormal right mastoid of Case 1 showing (→) relative radiolucency below the meatus due to erosion of the jugular fossa by tumor.

man subject (Case 1, R and L) due to the overlapping cervical spine. However, the dense areas below the meatus should normally be present, as noted on the dry skull "S" and the left mastoid of Case 1 (L). When the jugular fossa is destroyed, this increased density is no longer present (Fig. 4 R), and this finding should alert one to a possible glomus jugulare tumor.

REPORT OF A CASE

CASE 1. A 23 year old white male was feeling well until 4 months prior to admission when he began to notice the sound of his heart in his right ear as a "swishing" sound. Also, a few seconds of dizziness had been experienced once a week for the last 4 months. Physical and laboratory studies were not remarkable except for those of the right ear. The drum of the right ear was reddened but otherwise intact. The audiograms showed a hearing loss, predominantly of nerve origin. Hypofunction of the labyrinth was noted on the caloric examination.

Roentgen Findings: The right-sided carotid arteriogram failed to show any abnormality. The skull and mastoid series were not remarkable except for the modified Law's view. The submentovertex roentgenogram did not satisfactorily demonstrate the jugular foramen nor did it show any abnormality (Fig. 5). The

mastoid cells were clear and intact, indicating an early stage of the disease. The modified Law's view (Fig. 4 R) showed a relative radiolucency below the auditory meatus, when compared to the normal left side. The roentgenographic diagnosis was strongly suggestive of glomus jugulare tumor.

Operative Findings: At operation, the tumor was found to be localized to the jugular fossa area, eroding the surrounding bone, including the floor of the middle ear. The tumor was removed and the histologic diagnosis was glomus jugulare tumor. The patient recovered well from surgery.

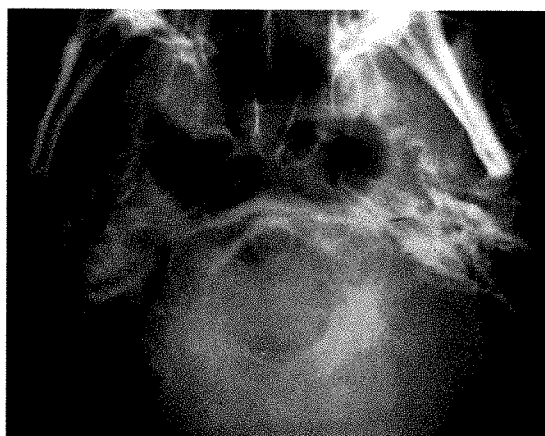


FIG. 5. Submentovertex view of Case 1 showing no apparent abnormality of the temporal bone.

Comment. The roentgenographic diagnosis of glomus jugulare tumor was possible before extensive bone destruction and mastoid changes occurred. The modified Law's projection was the only diagnostic view in this case, making possible the detection of early erosion of the jugular fossa. The open-mouth Waters' view was not obtained at that time; however, this view should also have demonstrated the erosion.

SUMMARY

A new roentgenographic technique is described by which to detect a glomus jugulare tumor in an early stage.

1. A modified open-mouth Waters' view gives good visualization of the jugular foramen, including the bony floor of the middle ear.

2. A modified Law's mastoid view demonstrates early erosion of the jugular fossa. A case of glomus jugulare tumor is reported as an example.

Seuk Ky Kim, M.D.
Department of Radiology
Duke University Medical Center
Durham, North Carolina

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NEW AND SIMPLE TECHNIQUES FOR DEMONSTRATION OF THE JUGULAR FORAMEN*

By JANE METZ STRICKLER, M.D.

BOALSBURG, PENNSYLVANIA

SINCE Guild⁶ first named and described the glomus jugulare in 1941 and Rosenwasser¹⁰ first recognized a tumor of this neuromyo-vascular tissue in 1945, diagnosis of tumor of the glomus jugulare has become important. The glomus jugulare tumor can arise from the sheath of cranial nerves IX or X or their branches or can originate from the adventitia of the jugular vein. These structures pass through the jugular foramen. In most published cases, no roentgenograms demonstrating the jugular foramen are included. Those that are shown exhibit far-advanced destruction from long-progressive tumor.

Since over 50 per cent of all glomus jugulare tumors originate in the adventitia of the jugular vein,⁹ study of the jugular foramen should be helpful in detecting these tumors earlier.

The French investigators^{2,3,4,7} have extensively roentgenographed the jugular foramina and have described the normal jugular canal as seen by laminagraphy.^{4,8} However, this author found their techniques complex to perform and difficult to reproduce. In the American literature the only adequate plain-film technique available is Eraso's¹ modified base view. The plain-film radiographic techniques for visualizing the jugular foramen to be presented here are reliable, reproducible and simple.

ANATOMY OF THE JUGULAR CANALS

The anatomy of the jugular foramen is illustrated in Figure 1. Gray⁵ divides the jugular foramen into 3 parts. The anterior part is the petro-occipital fissure which

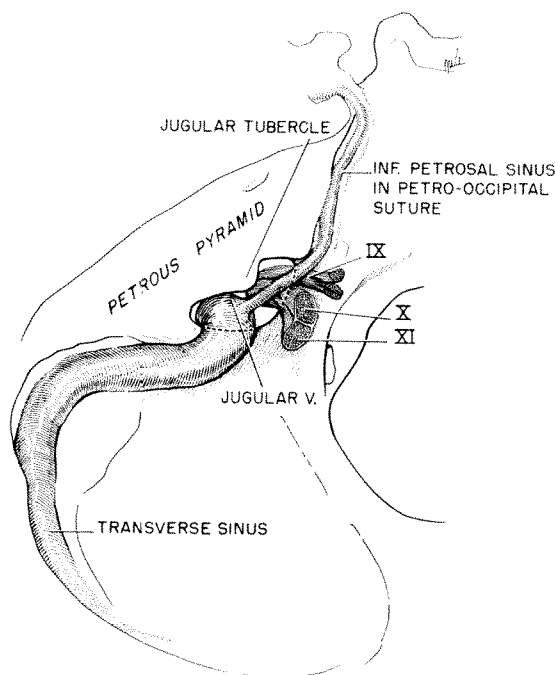


FIG. 1. Contents of the normal jugular foramen. Glomus jugulare tumors arise most often from the jugular vein adventitia, but can also arise from the sheath of cranial nerves IX, X or XI.

extends forward to the foramen lacerum. The remainder of the jugular foramen is the jugular fossa which is divided into 2 parts by a bony projection, the jugular tubercle. In the posterior portion, the transverse sinus becomes the jugular vein with its jugular bulb. In the anterior part of the fossa, the vagus (X) and spinal accessory (XI) nerves lie in a common sheath medially. The glossopharyngeal (IX) nerve lies anterolaterally. The inferior petrosal sinus follows the petro-occipital fissure and tra-

* Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October 1, 1965.

This work was done while the author was Assistant Staff Member (1963-1964) at Presbyterian University Hospital, Pittsburgh, Pennsylvania.

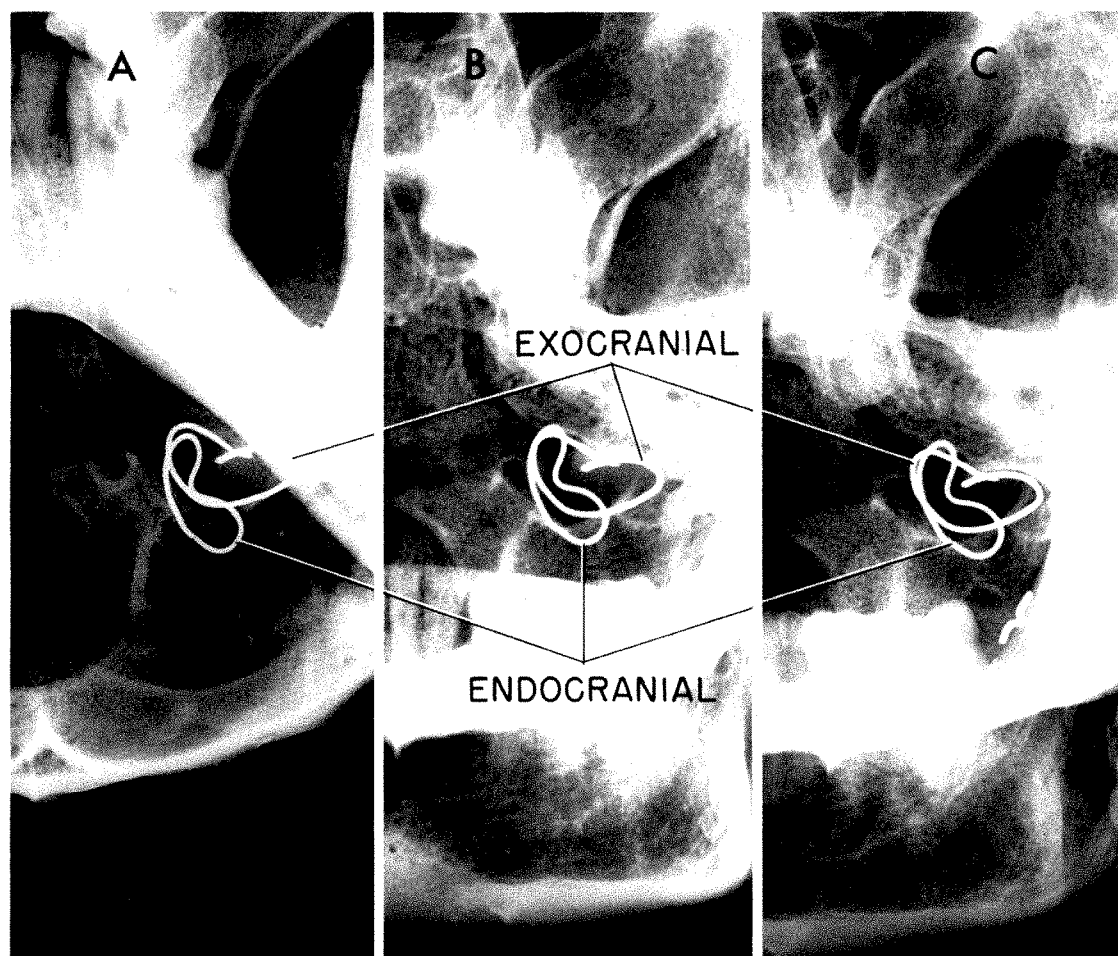


FIG. 2. Wire markers on the exocranial and endocranial openings of the jugular canal show progressively better visualization of the walls of the canal from (A) modified base view through (B) transoral view to (C) oblique open-mouth view. The canal is viewed truly "down the barrel" in C.

verses the jugular foramen lateral to the nerves to empty into the jugular vein.

The axis of the jugular canal from exocranium to endocranium runs in a postero-medial direction and lies posterior and perpendicular to the long axis of the petrous pyramid. Thus, an oblique open-mouth view should visualize the canal on end, or directly along its axis (Fig. 2A, B and C). This should be a good position for visualizing the walls of the canal by plain-film techniques or with laminagrams.

TECHNIQUES

Three plain-film techniques for visualization of the jugular foramen will be de-

scribed. The first 2 are transoral and oblique open-mouth views. The third is the author's method of obtaining Eraso's modified base view.

All 3 views are obtained by using the notch below the tragus of the ear (hereafter referred to as the infratragal notch) as a landmark for the location of the jugular foramen. The jugular foramina lie on a line connecting the right and left infratragal notch. Thus in the lateral view, the infratragal notch represents the position of the jugular foramen. Projection of the jugular foramen above, below or between any other easily discernible structure can be done precisely for each patient without regard to

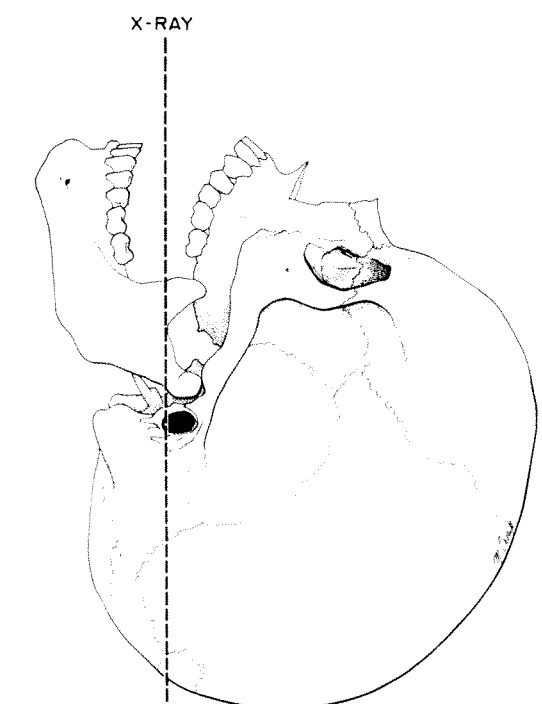


FIG. 3. Transoral projection. The x-ray beam perpendicular to the film passes between the molars and through the plane of the jugular foramina, which lies just caudad to the external auditory meatus at the infratragal notch.

any measured angles. This is done by aligning the central ray between the infratragal notch and the desired site of projection. The 3 techniques to be described use this principle and provide visualization of the

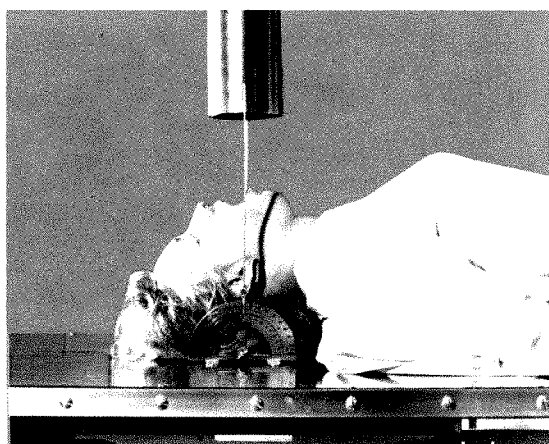


FIG. 4. Position for transoral projection viewed from side. X-ray beam passes through open mouth and infratragal notch of ear.

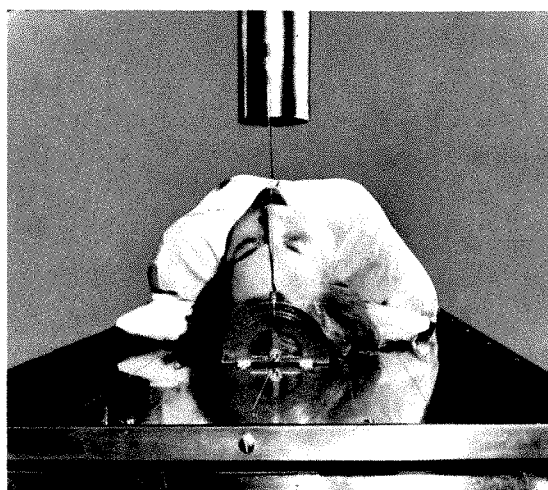


FIG. 5. Position for transoral projection viewed from head of table.

jugular foramen free from the interfering structure of the mandible, molars, mastoid air cells, and pyramid in each patient without use of measured angles.

TRANSORAL VIEW

1. Patient is supine with one pillow elevating his shoulders.
2. X-ray beam is perpendicular to the table and midline over the patient.
3. Patient has his mouth opened wide or

INF. PETROSAL SINUS IN PETRO-OCCIPITAL SUTURE

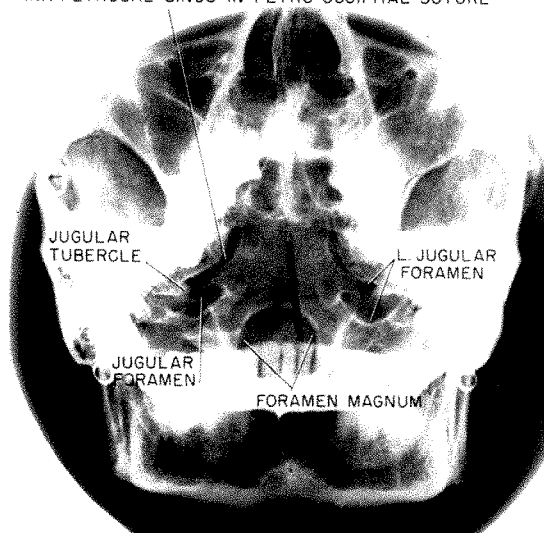


FIG. 6. Transoral view of both jugular foramina in a dry skull.

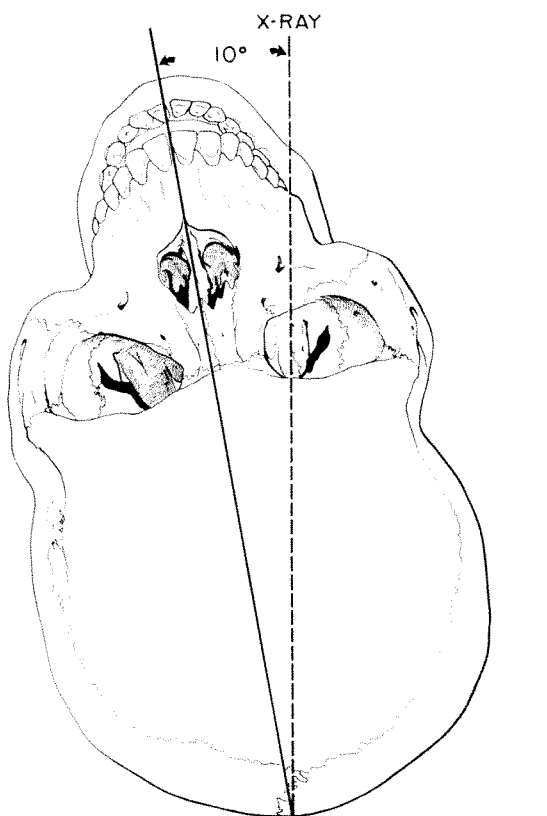


FIG. 7. Oblique open-mouth projection. When the face is turned 10° or less to the left from midline, the x-ray beam remains perpendicular to the film and becomes centered through the right jugular foramen.

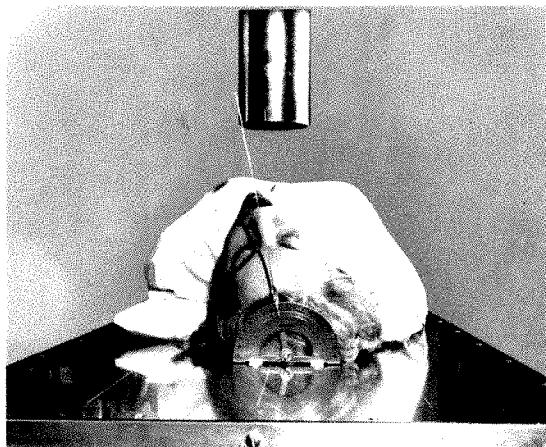


FIG. 8. Position for oblique open-mouth projection viewed from head of table. With chin and nose in a straight line, the face is rotated not more than 10° from midline to the left side for projection of the x-ray beam through the jugular foramen.



FIG. 9. Position for oblique open-mouth projection viewed from the side. With the face turned away from midline, the x-ray beam perpendicular to the table still passes through the gap between the molars and through the infratragal notch of the ear.

propped open with padded stick, cork, or other non-radiopaque object.

4. With patient's nose and chin in midline, extend or flex his head as necessary to align the central beam through the infratragal notch of the ear and the gap between the upper and lower molars as viewed from the lateral position. The position of this gap between the upper and lower molars can easily be palpated.

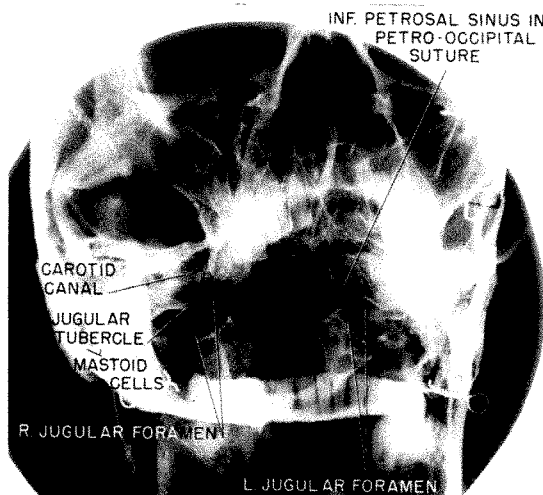


FIG. 10. Oblique open-mouth view of right jugular foramen in a dry skull. The walls of the jugular canal are clear and sharp in this "down the barrel" view.

5. Exposure factors are slightly less than those used for the base of the skull. In Presbyterian Hospital with parspeed screens, 36 inch target-film distance, Bucky diaphragm and extension cone, about 85 kvp. at 50 mas. were used for an average patient (Fig. 3, 4, 5 and 6).

OBLIQUE OPEN-MOUTH VIEW

1. Follow steps "1" through "4" above as for the transoral view.
2. Then, keeping the patient's chin and nose in a straight line parallel to mid-plane, roll patient's head 10° or less to one side. The exact angle of obliquity is not critical. This maneuver centers the x-ray over the jugular foramen and along the jugular canal on the side away from which the face is turned.
3. Repeat, turning the face to the opposite side, for the other jugular foramen (Fig. 7, 8, 9 and 10).

MODIFIED BASE VIEW

1. Patient is supine with pillows elevating his shoulders.
2. X-ray beam is perpendicular to the table and midline over the patient.

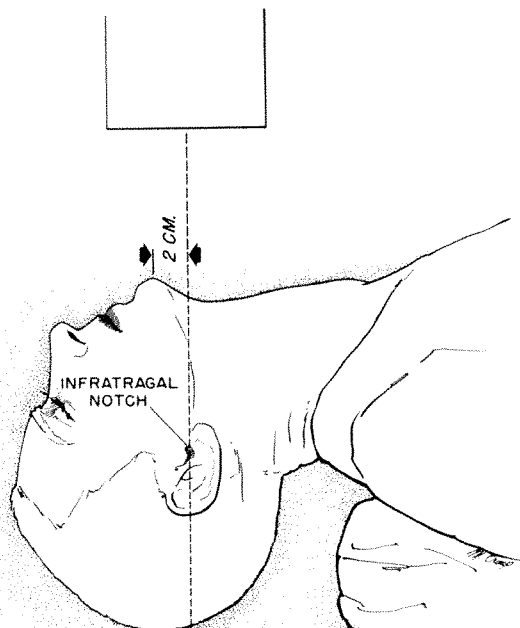


FIG. 11. Position for modified base view of both jugular foramina.

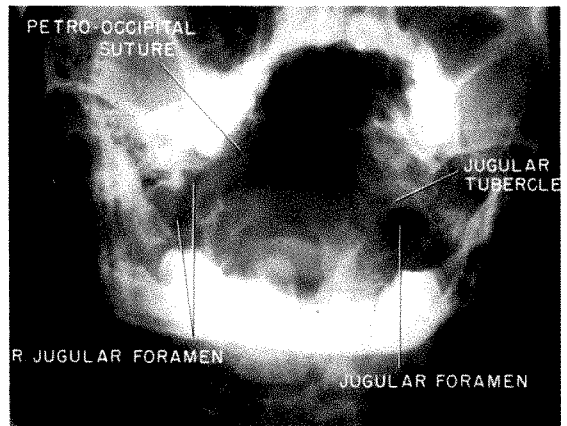


FIG. 12. Oblique open-mouth view of right jugular foramen in a normal patient.

3. With patient's mouth closed and nose and chin in midline, raise patient's chin until the central ray is aligned through (1) the infratragal notch of the ear and (2) a point 2 cm. caudad to the lower edge of the chin as viewed from the lateral position. There is no difference in positioning for edentulous patients (Fig. 11).

DISCUSSION

The three techniques for demonstrating the jugular foramina described here offer good visualization of the jugular canal and especially of the exocranial portion of the canal where the bulb of the jugular vein lies and where most of the glomus jugulare tu-

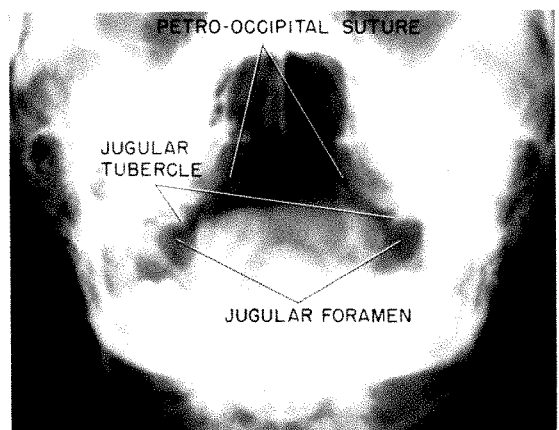


FIG. 13. Transoral view of the jugular foramina in the same normal patient.

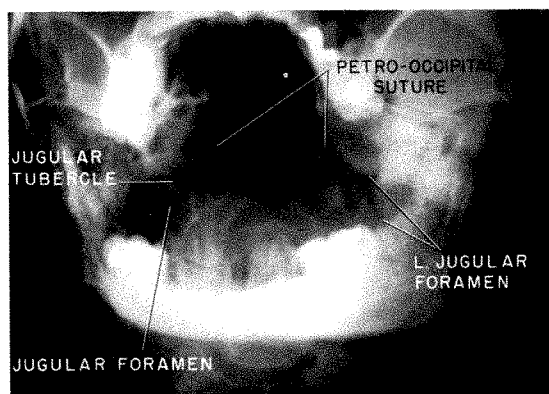


FIG. 14. Oblique open-mouth view of left jugular foramen in the same normal patient.

mors originate. The transoral view projects both foramina through the open mouth between the upper and lower teeth with the tongue medial and allows comparison of the two sides. The modified base view projects both foramina clear of the petrous ridges, which overhang anteriorly, and again allows comparison of the two sides. In the oblique open-mouth view, the jugular canal is projected between the tongue medially and the mastoid air cells laterally with the molars superior and inferior. The canal on the side away from which the face is turned is seen on end. The opposite jugular canal is seen at the same time across its axis (Fig. 12, 13 and 14).

These three techniques are easy enough to allow routine examination of the jugular foramen in all suspected cranial lesions. Much work comparing normal to abnormal jugular foramina should be done to discover if the wide variation of normal jugular foramina will limit seriously the interpretation of early changes in the abnormal jugular foramen. It is hoped that with these simple techniques available, many normal and, hence eventually, early abnormal jugular foramina will be examined. Perhaps then early glomus jugulare tumors originating at the jugular foramen may be detected.

SUMMARY

Three plain-film radiographic techniques for easy examination of the jugular foramina are described. The anatomy of the jugular foramen is illustrated. Perhaps use of these simple techniques for visualizing the jugular foramen will aid in early detection of tumors of the glomus jugulare.

Box 343

Boalsburg, Pennsylvania

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ORBITAL FRACTURES*

By MELVIN VINIK, M.D.,† and FREDIE P. GARGANO, M.D.‡
MIAMI, FLORIDA

THE roentgenologic evaluation of orbital fractures necessitates an orderly concept of the regional bone anatomy and its detailed roentgenographic appearance. Early diagnosis and treatment of such fractures may result in preservation of the patient's binocular vision and satisfactory cosmetic appearance.

Various symptom complexes following orbital fractures, with involvement of the soft intra-orbital parts, are common enough for the clinician to frequently recognize the site and type of fracture. This information is invaluable when pursuing the projection or procedure best suited to demonstrate the individual bony part and extent of fracture.

The roentgenography of orbital fractures is unlike that of other portions of the skeleton in that the bony surfaces are largely broad, exceedingly thin, and joined in a multangular relationship which renders their visualization on a single roentgenogram impossible.

The many clinical and anatomic classifications of orbital and periorbital fractures which exist attest to the almost unlimited combination of these fractures which may occur. The number, direction, and degree of traumatic forces applied will determine the type of fracture or fractures sustained.

It seems appropriate to evaluate orbital fractures according to their anatomic units or walls. Complex orbitofacial fractures are often those best evaluated clinically and roentgenographically, while the less obvious solitary wall fractures are frequently overlooked or misdiagnosed.

Although the routine roentgenographic projections of the facial bones and paranasal sinuses often suffice, we have found laminagraphy (sagittal and transverse), as well as positive contrast orbitography,

useful diagnostic adjuncts in selected cases of orbital fractures.

ANATOMY

The bony orbit is a pyramidal cavity with base (rim), apex, floor, roof, medial and lateral walls.³ The apex is directed posteromedially (Fig. 1, *A*, *B* and *C*).

- A. *Apex*: Optic foramen for optic nerve.
- B. *Floor*: Orbital plate of maxilla, orbital process of zygomatic bone, orbital process of palatine bone. Medially is the opening of the nasolacrimal duct. Running forward near the middle of the floor is the infra-orbital groove ending in front in the infra-orbital foramen.
- C. *Roof*: Orbital plate of frontal bone and small wing of the sphenoid. Medially lies the trochlea for the superior oblique muscle, laterally the lacrimal fossa.
- D. *Medial wall*: From anterior to posterior, the frontal process of maxilla, lacrimal, and ethmoid bones.
- E. *Lateral wall*: Orbital process of zygomatic bone and orbital surface of great wing of sphenoid.
- F. *Base*: Superiorly, supra-orbital arch of frontal bone; laterally, zygomatic bone and zygomatic process of frontal bone; inferiorly, zygomatic and maxillary bones; medially, frontal bone and frontal process of maxillary bone.

FRACTURES OF THE ROOF

Fractures of the frontal portion of the orbital rim are less common than one would expect due to the broad abutment at either end of the arch. Fractures laterally may involve the levator muscle of the upper lid;

* From the Department of Radiology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Florida.

† Resident in Radiology.

‡ Associate Professor of Radiology.

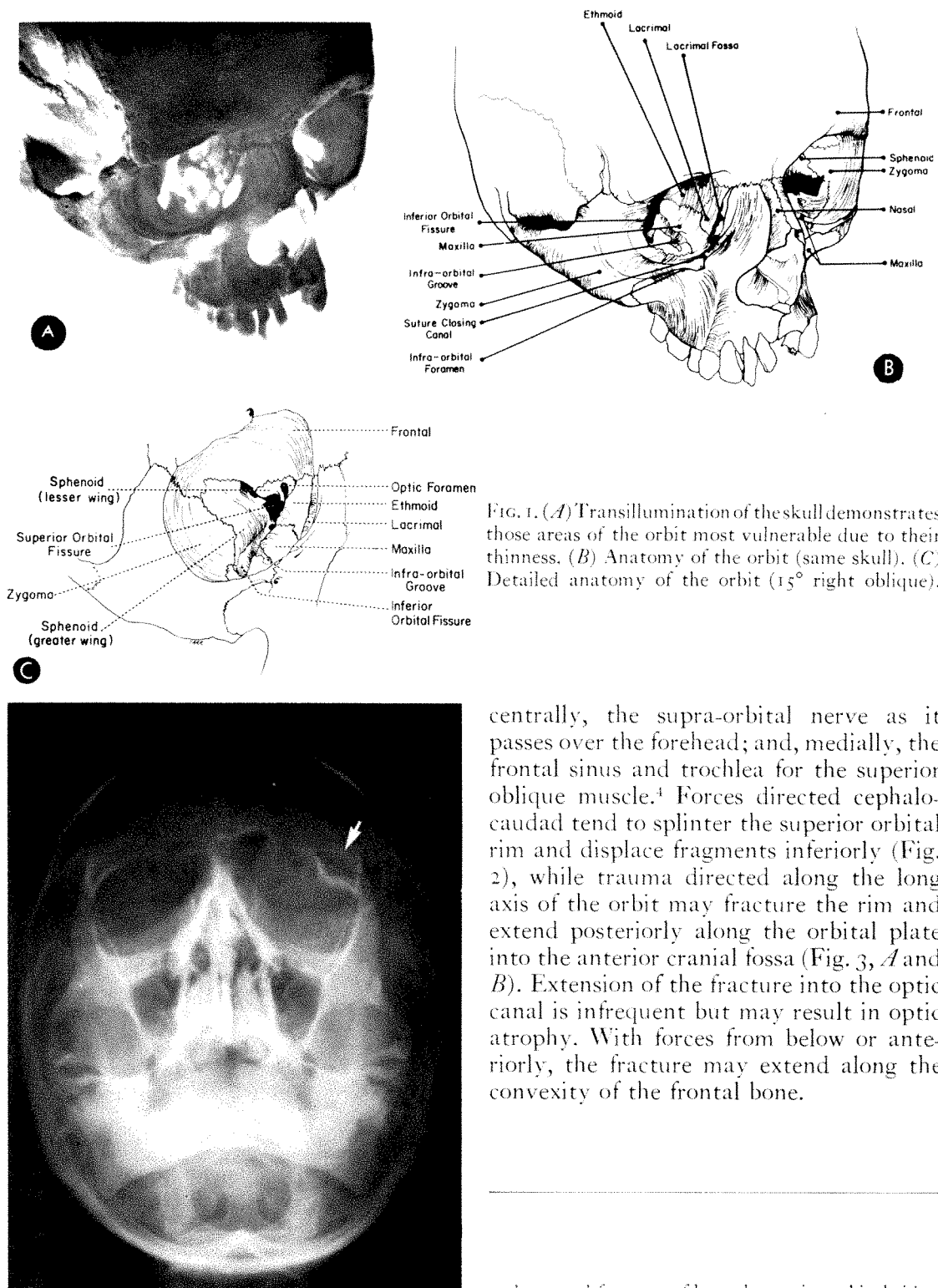


FIG. 1. (A) Transillumination of the skull demonstrates those areas of the orbit most vulnerable due to their thinness. (B) Anatomy of the orbit (same skull). (C) Detailed anatomy of the orbit (15° right oblique).

centrally, the supra-orbital nerve as it passes over the forehead; and, medially, the frontal sinus and trochlea for the superior oblique muscle.⁴ Forces directed cephalocaudad tend to splinter the superior orbital rim and displace fragments inferiorly (Fig. 2), while trauma directed along the long axis of the orbit may fracture the rim and extend posteriorly along the orbital plate into the anterior cranial fossa (Fig. 3, A and B). Extension of the fracture into the optic canal is infrequent but may result in optic atrophy. With forces from below or anteriorly, the fracture may extend along the convexity of the frontal bone.



FIG. 2. This 65 year old patient sustained trauma to left superior orbital ridge. Roentgenogram shows

depressed fracture of lateral superior orbital ridge. This fracture was not visible on the posteroanterior skull roentgenogram.

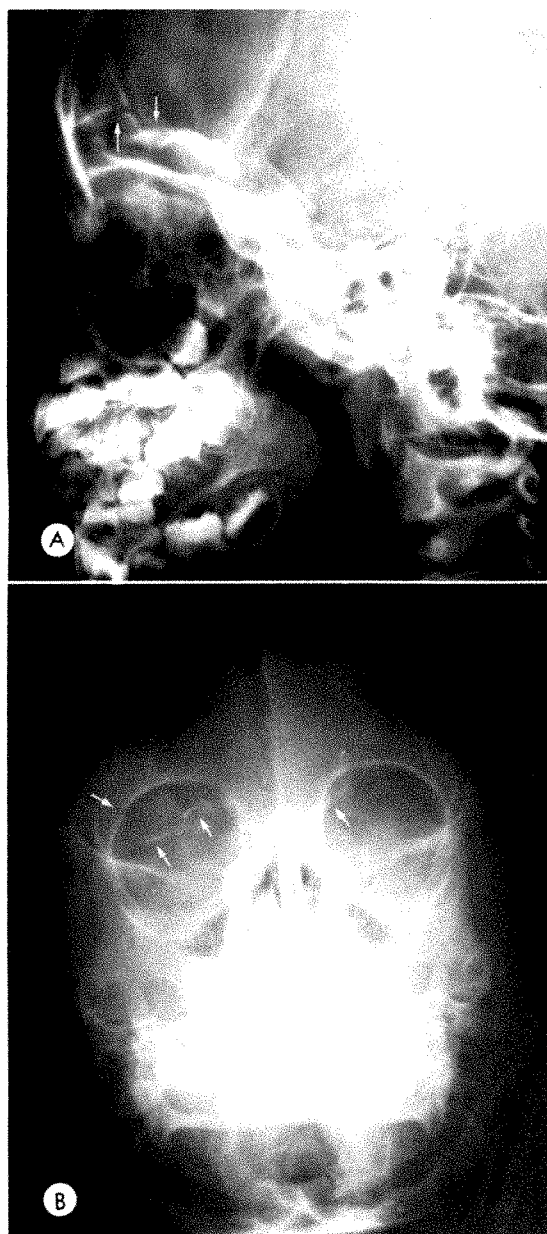


FIG. 3. This 4 year old child fell from a two story building and landed on his face. Marked swelling in the right supra-orbital region and nosebleed were present. (A) A depressed fracture at the nasofrontal suture and a comminuted fracture of the right orbital roof (floor of the anterior fossa) are present. Note buckling of the roof. (B) On the Waters' projection, the fracture is seen to extend to the superolateral rim of the right orbit. Roof fragments seen on end are noted in the right orbit and medial portion of the left, indicating extension to this side across the cribriform plate. Decompression of the right orbit was performed with removal of the comminuted fragments.



FIG. 4. This 68 year old man was hit with a pistol about the right orbit. Oblique roentgenogram of the orbit demonstrates a diastatic fracture at the zygomatic frontal and zygomatic sphenoidal sutures. A roentgenogram in the Waters' projection was normal.

FRACTURES OF THE LATERAL WALL

The strongest portion of the rim is the lateral margin which is subjected frequently to trauma directed to the malar eminence of the zygoma, the area of greatest prominence in the cheek. Fracture of the lateral wall is an indication for adequate roentgenographic study of the zygomatic arch. The direction of trauma in lateral wall fractures can be inferred by evaluating the degree of depression, cephalad or caudad displacement of the zygomatic arch and

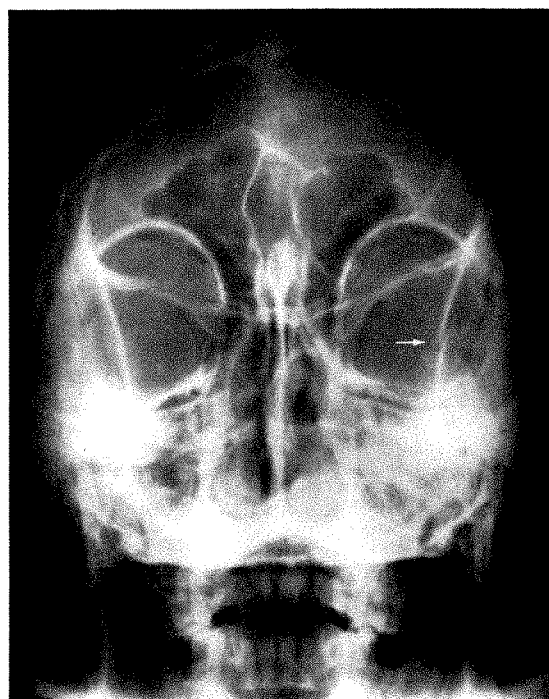


FIG. 5. This 45 year old man received a blow to the left frontotemporal region. On the roentgenogram, the left innominate line is interrupted, indicating a fracture of the posterolateral orbital wall.

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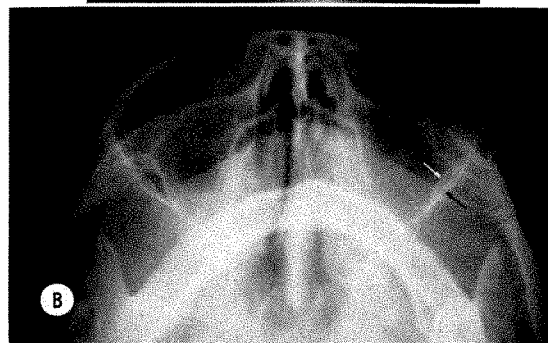
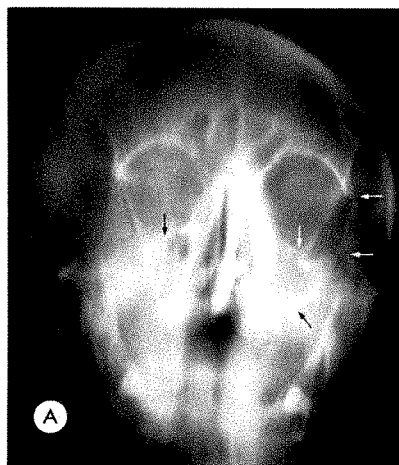


FIG. 6. This 58 year old man was severely beaten about the face and head. On admission to the

malar eminence. Frequently, the trauma is of sufficient degree to fracture the lateral wall and floor of the orbit as well as the lateral wall of the maxillary sinus, resulting in a floating malar bone or "tripod" fracture (Fig. 4; 5; 6, *A* and *B*; and 10, *A* and *B*). The zygomatic bone is vital to the lateral and inferior support of the globe. These fractures may involve the lacrimal gland and can cause limitation of mandibular mobility and pain if the depressed zygomatic arch impinges upon the coronoid process of the mandible. The insertion of the lateral canthal ligament to the zygoma accounts for distortion of the outer canthus sometimes seen with lateral wall fractures.

FRACTURES OF THE MEDIAL WALL

Fractures of the paper thin orbital portion of the ethmoid (lamina papyracea) certainly occur more frequently than is recognized.

The medial walls of both orbits can be

hospital, a massive ecchymosis about the left orbit was present; the lids were swollen shut. (*A*) Laminogram in the Waters' view demonstrates a "tripod fracture" of the left orbit. In laminograms the margins of the normal infra-orbital groove and foramen often appear as two linear bony projections thrust inferiorly toward the antrum (arrow right orbit); this finding should not be mistaken for fracture of the orbital floor. (*B*) The basal view again confirms the presence of inferior rim and malar fractures. Contrast the indistinct orbital line (dark arrow) and altered antral line (white arrow) to the normal right side.⁵

FIG. 8. This 46 year old female was kicked in the face and admitted to hospital with double vision and limited upward gaze in the left eye. There were left enophthalmos and hyperesthesia in the left infra-orbital region. Roentgenogram shows a blow-out fracture of the left orbital floor with "hanging drop sign." The depressed bone fragments should not be confused with the lateral extension of the sphenoid sinus cell walls which may normally be superimposed near the floor of the orbit.



considered as limiting the lateral margins of the inter-orbital space. The roof of this space is the cribriform plate and within the space lie the ethmoid sinuses, the upper and middle turbinates, and the bony nasal septum (Fig. 10C). The nasal bones protect this space, but if they are fractured, there is little to prevent the underlying septa from collapse (Fig. 7). Similar fragmentation and displacement of the medial wall may occur with fractures of the abutments superiorly of the frontal bone and inferiorly of the maxilla.

The thinness of the medial wall also predisposes it to fracture when the hydraulic intra-orbital pressure is suddenly increased. This mechanism is similar to that seen in blow-out fractures of the floor; indeed, blow-out fractures of the floor and



FIG. 7. This 50 year old man was struck in the face with a block of ice. He complained of excessive tearing from right eye. The Waters' projection demonstrates a 2 cm. length of nasolacrimal bone displaced medially in its inferior portion.

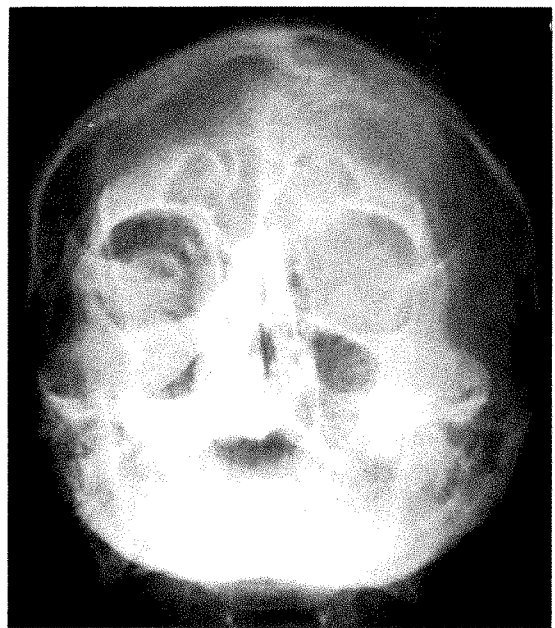
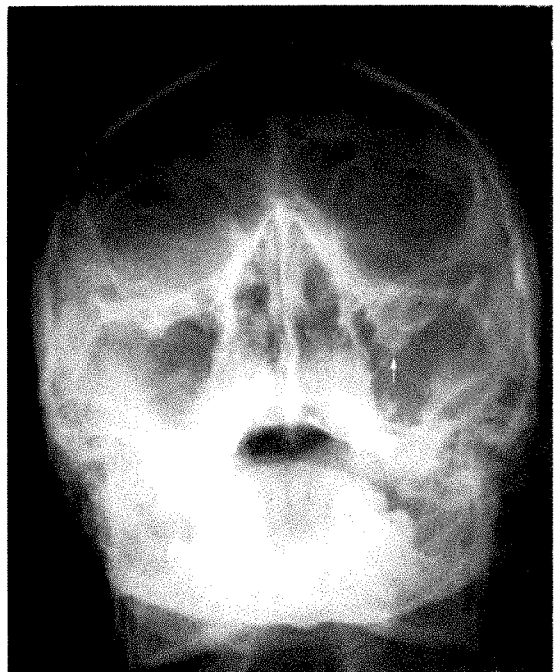


FIG. 9. This 65 year old man was punched in the right eye. Limited upward gaze, crepitation and bubbles in the conjunctiva were noted upon examination. Roentgenogram shows a traumatic orbital pneumogram and a soft density projecting into the maxillary sinus. At surgery, the entire floor of the orbit was "blown-out." Compound fracture to the exterior or extending into any of the paranasal sinuses may produce a traumatic orbital pneumogram.

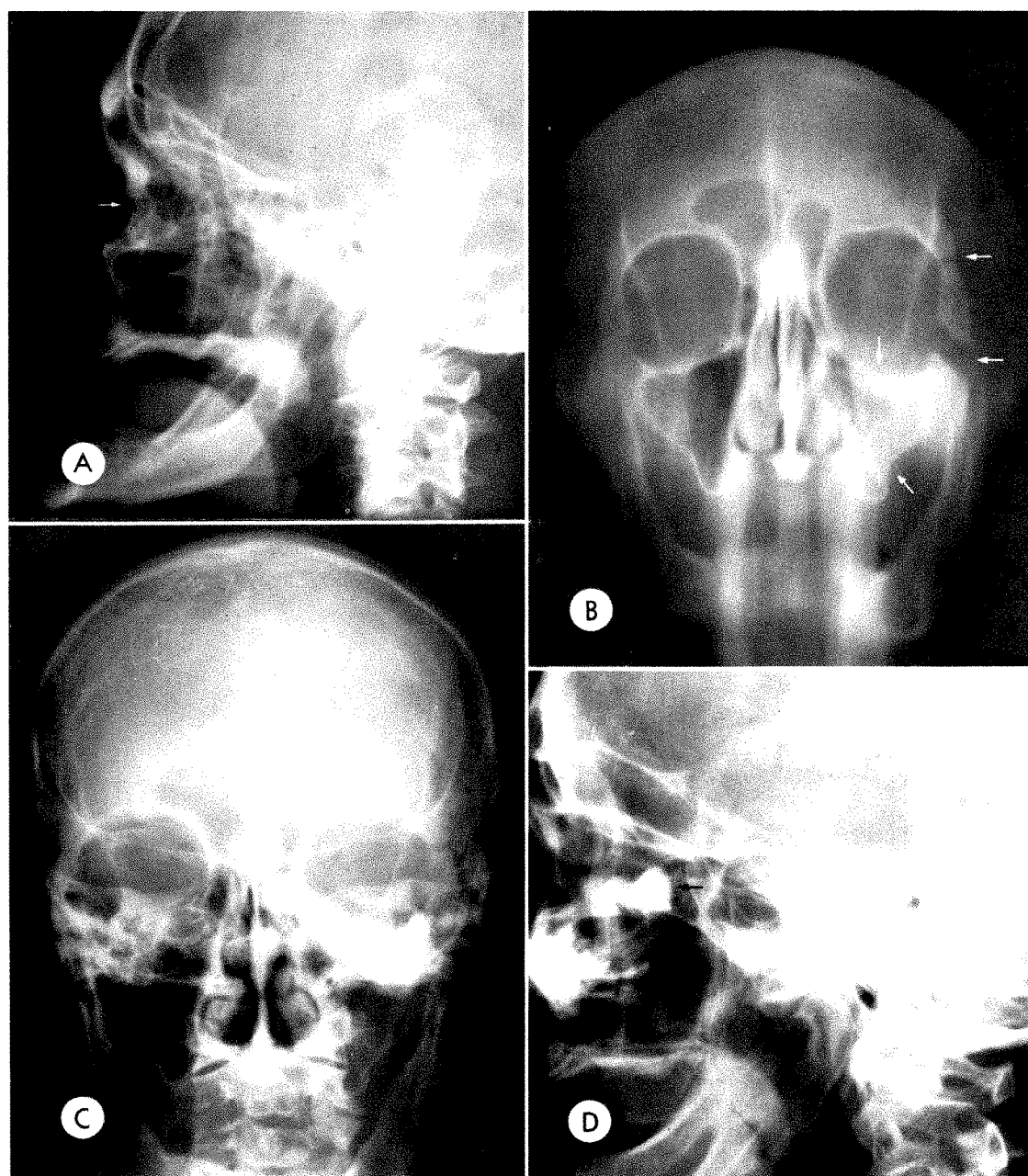


FIG. 10. This 59 year old man was beaten about the head and face. The left lids were ecchymotic and closed. (A) Lateral roentgenogram shows an irregular "step" in the lateral orbital rim. Compare to the smooth margin of the opposite side. (B) Laminagram shows the lateral rim fractures and the medially displaced lateral wall of the maxillary sinus. A hazy density is superimposed over the orbital floor. (C) Water soluble contrast medium was introduced between the bony orbital floor and globe. Some contrast medium has entered the inter-orbital space. (D) The contrast medium is localized to an air cell in the ethmoid sinus and a small amount has trickled into the maxillary antrum, indicating a fracture of the orbital floor. The bulk of contrast medium below the level of the orbital floor represents leakage into the soft tissues about the malar eminence and inferior rim. At surgery, the orbital floor was fractured in several areas with herniation in each. A fracture of the ethmoid was confirmed.

medial wall are frequently associated (Fig. 10D).

The lacrimal sac and insertion of the medial canthal ligament lie along the medial wall anteriorly near the junction of the lacrimal bone and frontal process of the maxilla. Fractures here may distort the medial canthus and disturb lacrimal drainage. If the cribriform plate is involved cerebrospinal fluid rhinorrhea may result.

FRACTURES OF THE FLOOR

The contributions of Converse and Smith¹ in the diagnosis and treatment of blow-out fractures of the floor are noteworthy. They described in detail how blunt orbital trauma may increase intra-orbital pressure with rupture of the thin postero-medial portion of the floor, displacement inferiorly of the bony fragments and herniation of the orbital contents. The portion of the floor typically blown out is further weakened by the infra-orbital groove. Herniation and incarceration of the inferior oblique muscle account for the classic finding of limited upward gaze. Protrusion of the orbital fat pad through the defect may cause enophthalmos.

As originally described in the "pure" form, this type of fracture was a solitary finding, but since then it has been shown to occur with rim and other wall fractures, the common denominator being increased intra-orbital pressure (Fig. 8 and 9).

Fractures of the floor with no displacement of fragments into the maxillary antrum may occur in continuity with fractures of the inferior rim as well as of the medial and lateral walls (Fig. 6, A and B; and 10, A-D). The clinical features of blow-out fractures of the floor: *i.e.*, (1) inability to elevate the globe; (2) vertical diplopia;

and (3) peri-orbital ecchymoses, occur in 90 per cent or more of affected patients.²

The diagnosis is confirmed by the roentgenographic findings of: (1) fragmentation of the bone of the orbital floor; (2) depression of the bone fragments; and (3) prolapse of orbital content into the maxillary antrum.

SUMMARY

Roentgenographic and clinico-anatomic features of orbital fractures are described with emphasis upon orderly evaluation of the four walls involved.

Clinical signs associated with orbital fractures are related to altered anatomy. An appreciation of these factors is invaluable in the choice and evaluation of roentgenographic procedures best suited for confirmation of the suspected injury.

Department of Radiology
University of Miami
School of Medicine
Jackson Memorial Hospital
Miami, Florida 33136

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THE ROENTGENOLOGIC EVALUATION OF ORBITAL BLOW-OUT INJURIES*

By GERHARD F. FUEGER, M.D., ALBERT T. MILAUSKAS, M.D., and
WILLIAM BRITTON, M.D.

BALTIMORE, MARYLAND

BLOW-OUT injuries of the orbit, although largely unrecognized prior to the classic communication of Smith and Regan³ in 1957, are now well known entities. These fractures, which may occur in either the floor or the medial wall of the orbit, result from a blow to the eye by a blunt object. The force of the blow, transmitted by the closed hydraulic system of the eyeball, causes a sudden increase in the intraorbital pressure. In blow-out fractures this pressure is released by the expulsion of orbital soft tissues, *i.e.*, fat, muscle or both, through points of low resistance in the inferior or medial walls of the orbit. If the trapped soft tissue is not reduced surgically, permanent diplopia develops in a large number of cases. The preoperative diagnosis of blow-out fracture is, therefore, important but it is often difficult by conventional methods.

The roentgenologic techniques ordinarily advocated for the evaluation of patients with suspected blow-out injury are plain roentgenograms in Waters' and Caldwell's positions, and tomography^{1,2,4}

In an anatomic study we have found that the floor of the orbit is not a simple plane but consists of two distinctly different regions: an anterolateral plane portion and a posterior portion that bulges upward. These two regions, despite their different configurations, cannot be distinguished one from the other on either Caldwell's or Waters' views. We have, therefore, developed a special posteroanterior view of the skull (Fig. 1) which permits identification and evaluation of the separate portions of the orbital floor. This view for the profile of the orbital floor is obtained by placing the patient's head in the nose-brow position; a

posteroanterior roentgenogram is then made with the central ray angulated 30 degrees caudally so that it exits approximately 1 inch below the nasion. In addition, a special 20 degree oblique view, obtained by placing the injured orbit directly on the cassette and angling the central ray 35 degrees caudally through it (Fig. 2), has been most helpful in evaluating the lateral half of the orbital floor and the underlying facial bones.

METHOD OF STUDY

In a clinical study these two new views of the orbit, with and without the utilization of contrast injections, have been used to evaluate cases of suspected blow-out injury. Patients in this group were studied additionally with routine views of the orbit (Waters', Caldwell's, and lateral) and occasionally tomography, too (Fig. 3 through 5).

Positive contrast orbitography was

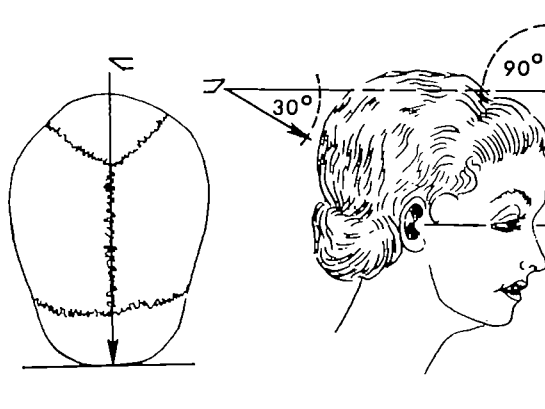


FIG. 1. Special view I. Projection for the profile of the floor of the orbit (30° posteroanterior). Schematic representation of patient positioning and beam direction. The patient's head is posteroanterior; the floor of the orbit is oblique.

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From the Johns Hopkins Medical Institutions, Department of Radiology and Department of Ophthalmology, Baltimore, Maryland.

achieved by injection of 6 ml. of a special preparation along the inferior wall of the orbit, external to the muscle cone. The isotonic contrast mixture was compounded of 3.5 ml. of 50 per cent sodium diatrizoate (hypaque 50 per cent), 3.0 ml. of 2 per cent lidocaine (xylocaine), and 0.5 ml. of diluent containing 300 units of hyaluronidase (wydase). To date, we have carried out 75 orbitographies and have observed no single untoward reaction or incident; on 3 occasions contrast material was injected inadvertently into the intraconal space without ill effects.

PATIENT MATERIAL AND RESULTS

One hundred and twenty-seven patients with facial injury were studied between July, 1962 and December, 1964. Of these, 58 were clinically suspected of having a blow-out injury because of the clinical finding of diplopia in the absence of anterior facial fractures. These 58 patients were examined by the following methods: routine views, 58 patients; "special" views, 42 patients; tomography, 35 patients; and orbitography, 40 patients.

The 58 patients were ultimately categorized as follows: 30 had fractures limited to

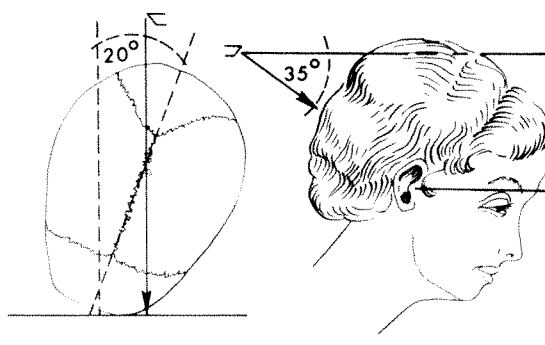


FIG. 2. Special view II. Projection for the profile of the anterolateral segment of the orbital floor (20°/35° oblique). Schematic representation of patient positioning and beam direction. The head is oblique; the orbital floor is posteroanterior. The glabellomeatal line is used as baseline, rather than the canthomeatal line. Orienting the latter line perpendicularly would place the frequently swollen orbital soft tissues directly on the film support, which is quite painful and undesirable.

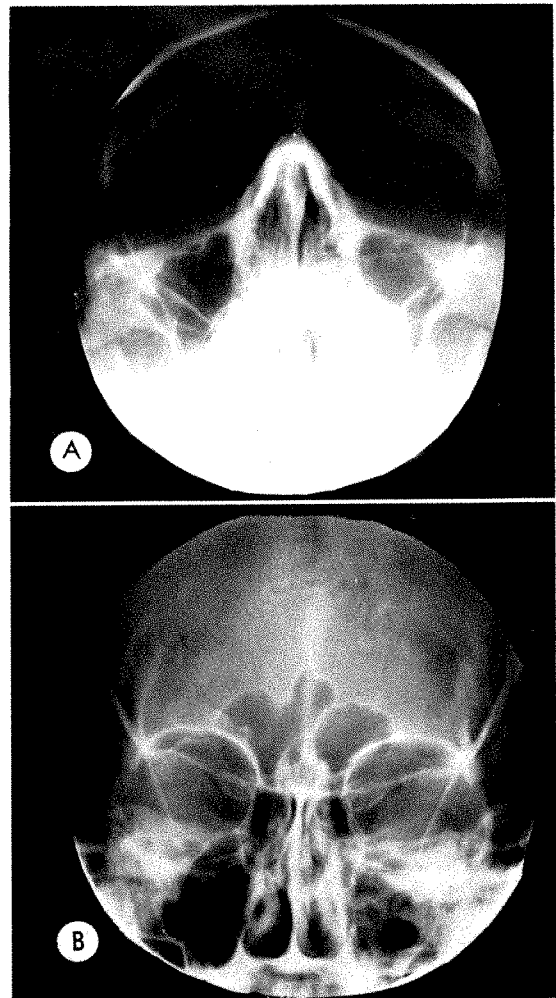


FIG. 3. Case 1. (A) Waters' view. Surgically proven blow-out fracture of the left orbit. Diffuse opacification of the maxillary sinus. The injury is not recognizable. (B) Caldwell's view. The orbital floor is obscured by the petrous ridge of the temporal bone. The fracture is not discernible.

the orbital floor, 5 had fractures limited to the medial wall of the orbit, 13 had fractures involving both the floor and the medial wall, 5 had fractures of the orbital floor extending into the orbital rim, and 5 had no fractures.

Eighteen of the patients with surgically proven blow-out injuries were studied preoperatively by all four methods (routine views, "special" views, tomography, and orbitography). The comparative results are shown in Table I.

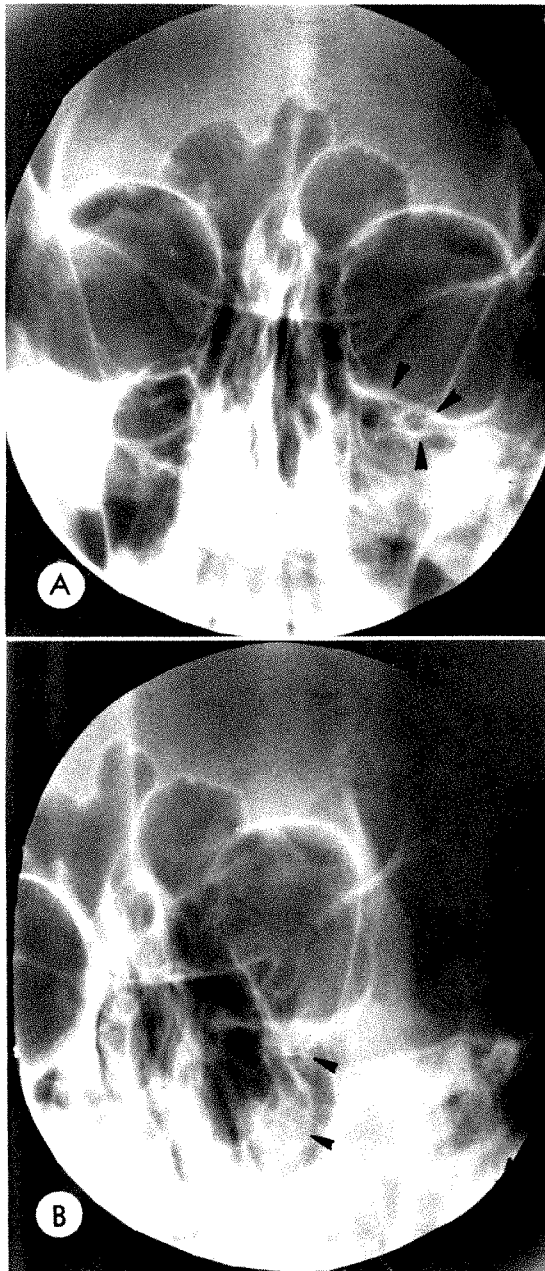


FIG. 4. Case 1. (A) Special view I (30° posteroanterior). The surgically proven blow-out fracture is on the left side; the contours of the orbital floor are interrupted (upper arrows) and a large bone fragment is displaced in the maxillary sinus (lower arrow). The contours of the uninjured, right orbital floor are distinct and intact. The upper convex line represents the posterior bulging of the orbital floor; the lower line represents the anterior portion. (B) Special view II ($20^\circ/35^\circ$ oblique). The bone fragment and the herniation of orbital tissues are seen "on-end" (upper arrow). A rounded soft-tissue shadow (lower arrow) is discernible in the maxillary sinus.

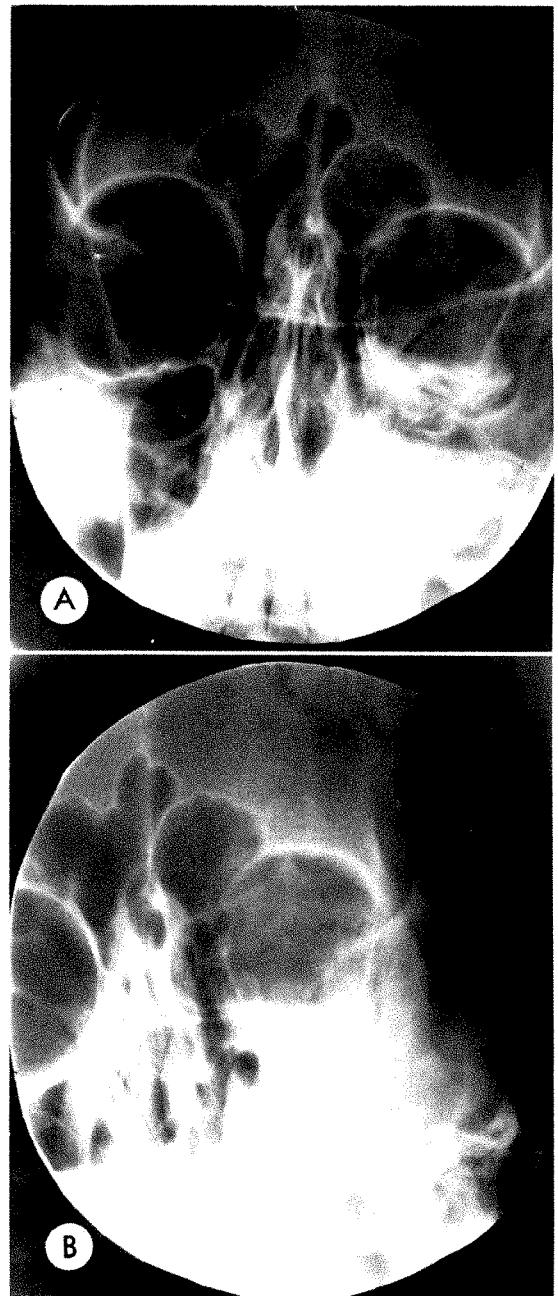


FIG. 5. Case 1. (A) Special view I, after contrast injection. (B) Special view II, after contrast injection. Note contrast material in the maxillary antrum in each view.

DISCUSSION

Orbitography is the most reliable method in the roentgenographic demonstration of orbital blow-out fractures. The contrast material passes through the traumatic defects and is easily visualized in adjacent sinuses.

TABLE I
EIGHTEEN SURGICALLY PROVEN
"BLOW-OUT" FRACTURES

Method of Study	Interpretation		
	Fracture	Un- certain	No Fractures
Routine views	1 (5%)	8 (45%)	9 (50%)
"Special" views	16 (80%)	2 (11%)	0
Tomography	11 (61%)	2 (11%)	2 (28%)
Orbitography	18 (100%)	0	0

Initially, our attention was focused on the orbitographic findings. Later, it became apparent that most of the injuries could be observed in the special views without the addition of a contrast material. In our experience, the routine roentgenographic views were remarkable only because of the paucity of findings in many proven cases of blow-out fracture.

Linear tomography fell far short of its expected value in the discovery of blow-out injuries of the orbit. Hypocycloid tomography promises a much higher range of accuracy, but our experience with this method is still too limited to permit a fair evaluation.

The useful signs of orbital blow-out fractures as demonstrated by the special 30 degree posteroanterior view are: (1) absence of the anterior orbital line with a "pseudopolyp" in the roof of the antrum as a result of herniation of orbital contents; (2) divergence of the two lines representing the orbital floor; (3) a defect in the posterior bulge of the orbital floor; (4) depression of the posterior bulge of the orbital floor; (5) a bone fragment in the maxillary antrum below the lines of the orbital floor; (6) diffuse widening and opacification of the contours of the orbital floor; (7) asymmetry of the ethmomaxillary septum; (8) opacification of the inferomedial air cells; (9) fragmentation of the medial orbital wall; (10) opacification of all or part of the ethmoid sinuses; and (11) orbital emphysema.

The signs of orbital blow-out fracture in Waters' and Caldwell's views are frag-

mentation; depression or prolapse of the orbital floor; fracture of the inferior orbital rim; fracture of the medial orbital wall; opacification of the maxillary antrum; and orbital emphysema.⁴

In our experience, these changes often are not apparent on routine views in cases of minimal-to-moderate orbital blow-out injury. On the other hand, we are impressed that the minor changes representing small fractures and minimal herniation are easily perceived on the "special" views or with positive contrast orbitography.

SUMMARY

Positive contrast orbitography was found to be a safe, simple, and highly accurate method of demonstrating blow-out fractures of the orbit. Two new views were devised, one for a profile of the orbital floor and the other for the anterolateral segment of the orbital floor. These new views, without contrast material injection, allowed recognition of orbital blow-out fractures in 80 per cent of the cases in a surgically proven series. Tomography, and conventional Caldwell's and Waters' views, provided less findings for evaluating the integrity of the medial wall and floor of the orbit.

Gerhard F. Fueger, M.D.
Department of Radiology
Johns Hopkins Medical Institutions
601 N. Broadway
Baltimore, Maryland

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INTERNAL ORBITAL FRACTURES: THE VALUE OF LAMINAGRAPHY IN DIAGNOSIS*

By HOWARD R. GOULD, MAJOR, USAF, MC, and CHARLES O. TITUS, MAJOR, USAF, MC
WIESBADEN, GERMANY

THE method of production of so-called "blow out" fracture or internal orbital fracture has been adequately discussed in the literature.^{2,3,4,5,11,12} The majority of authors feel that these fractures are caused by a blow, the force of which is transmitted through the globe to the walls of the orbit. Since the floor of the orbit is the thinnest wall, this is the most frequently fractured. The medial wall or ethmoid plate is the next most frequent site of fracture. The problems of a missed fracture of the orbit are mostly involved with fractures of the floor. Late sequelae of this type fracture include: (1) enophthalmos, creating a severe cosmetic defect; (2) persistent diplopia; and (3) a frozen eye, incapable of moving in any direction (Fig. 1). Fractures into the ethmoid or maxillary sinuses are also a potential cause of orbital cellulitis.

The literature varies with respect to the value of different types of roentgenographic examination in injuries to the orbit. Some authors^{2,4,5,7,8,9} stress the values of laminagraphy, while others¹¹ consider it of little value. In an effort to determine the diagnostic accuracy of the various types of examination, each patient had a clinical examination by an ophthalmologist, routine roentgenograms (posteroanterior, lateral and stereoscopic Waters' projections), and in most case laminagraphy, performed in the posteroanterior and lateral positions. Single cuts, at 1 cm. intervals, with a 40 inch target film distance and 55 degrees amplitude of rotation were used on the laminagrams.

Cases with fractures of the orbital rim and zygomatic eminences were excluded. One of the included cases also had a fracture of the anterior surface of the maxilla in



FIG. 1. Fracture of the floor of right orbit of 2 months' duration. The patient now presented with enophthalmos, downward displacement of the globe and diplopia on upward gaze. (A) Level gaze. (B) Upward gaze. Corrective surgery at this time was unsuccessful. This patient is not included in the data in this paper, since he was initially seen at another hospital.

addition to the floor of the orbit. In the literature, Cunningham and Marden⁵ mention that a blow from a fist is the most common cause for this type injury, and is usually present in about 60 per cent of the cases. In our series of 21 cases, 38 per cent were due to a blow by a fist, and 31 per cent were due to a blow by a foot (Table I).

TABLE I
CAUSES OF INJURY
(21 CASES)

Cause of Injury	No. of Cases
Hit by Fist	8
Kicked by Foot	6
Flying Object	3 (1 snowball, 1 softball, 1 bottle)
Fell on Object	3 (1 bedpost, 1 doorsill, 1 automobile)
Automobile Accident	1

* From the Radiology and Ophthalmology Services, United States Air Force Hospital, Wiesbaden, Germany.

The views expressed herein are those of the authors and do not necessarily reflect the views of the U. S. Air Force or the Department of Defense.

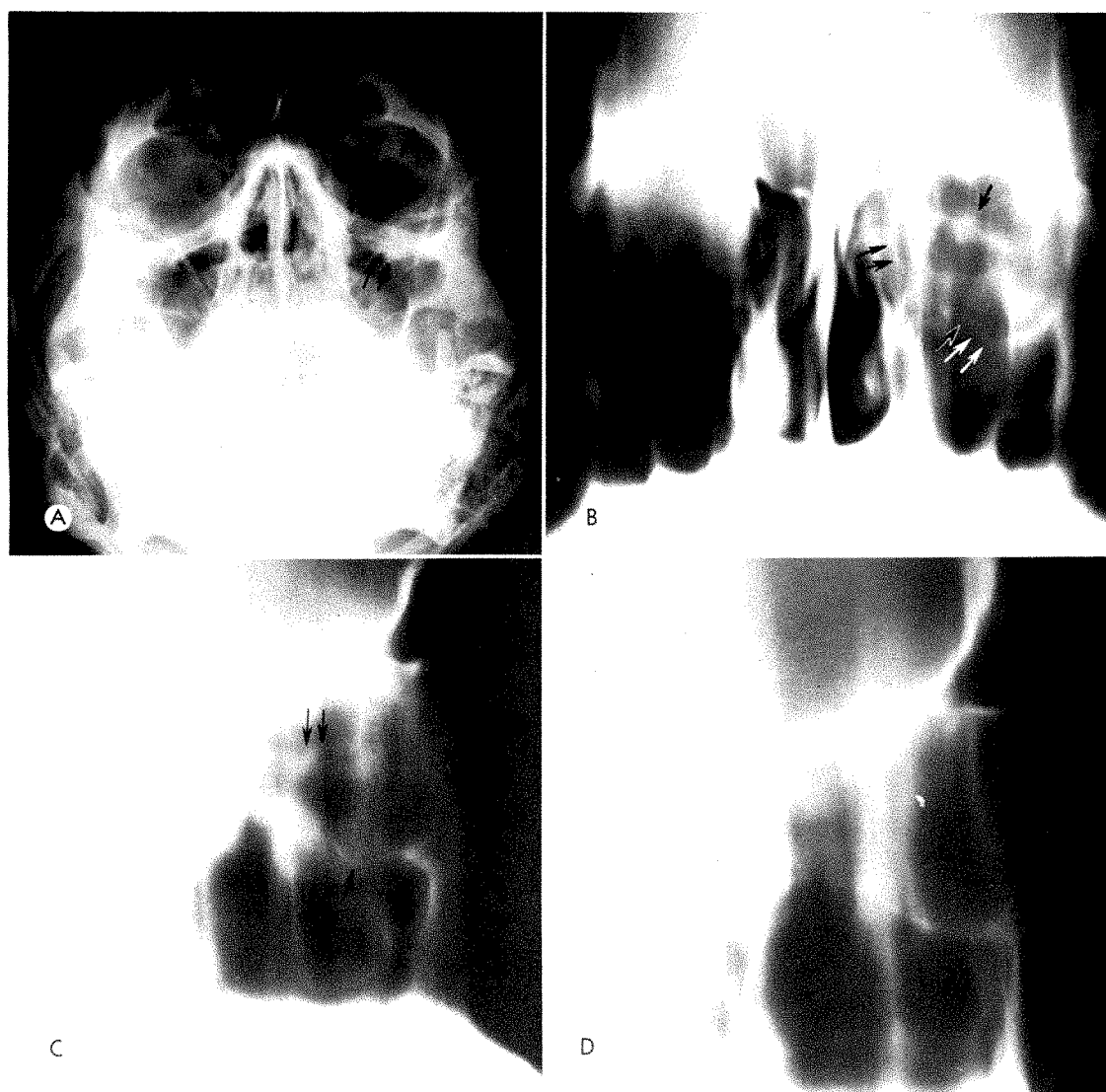


FIG. 2. Patient fell on bedpost and had diplopia on upward gaze. (A) Waters' view shows left orbital emphysema (single arrow). The fracture site was missed on initial reading, but review of roentgenograms showed a small soft tissue density in roof of left antrum and slight downward protrusion of orbital floor (double arrow). (B) Posteroanterior laminagram shows air around optic nerve (single arrow), fracture of ethmoid plate (double arrow), and buckled floor of orbit (triple arrow). (C) Lateral laminagram of left orbit shows buckled floor (single arrow) and air around optic nerve (double arrow). (D) Lateral laminagram of normal right orbit for comparison.

Our criteria for diagnosis were as follows:

1. Clinical diagnosis was made when one of the following findings was present after trauma to the orbit: (a) persistent diplopia; (b) limitation of movement of the globe; (c) downward displacement of the globe; (d) enophthalmos or proptosis; (e) palpable emphysema; and (f) diminished or absent

sensation of the infraorbital nerve—not an absolute sign.

2. The roentgenographic diagnosis of a fracture depended upon visualization of a displacement or interruption of bone in one of the orbital walls. Secondary signs of fracture included orbital emphysema, clouded ethmoid or maxillary sinus and

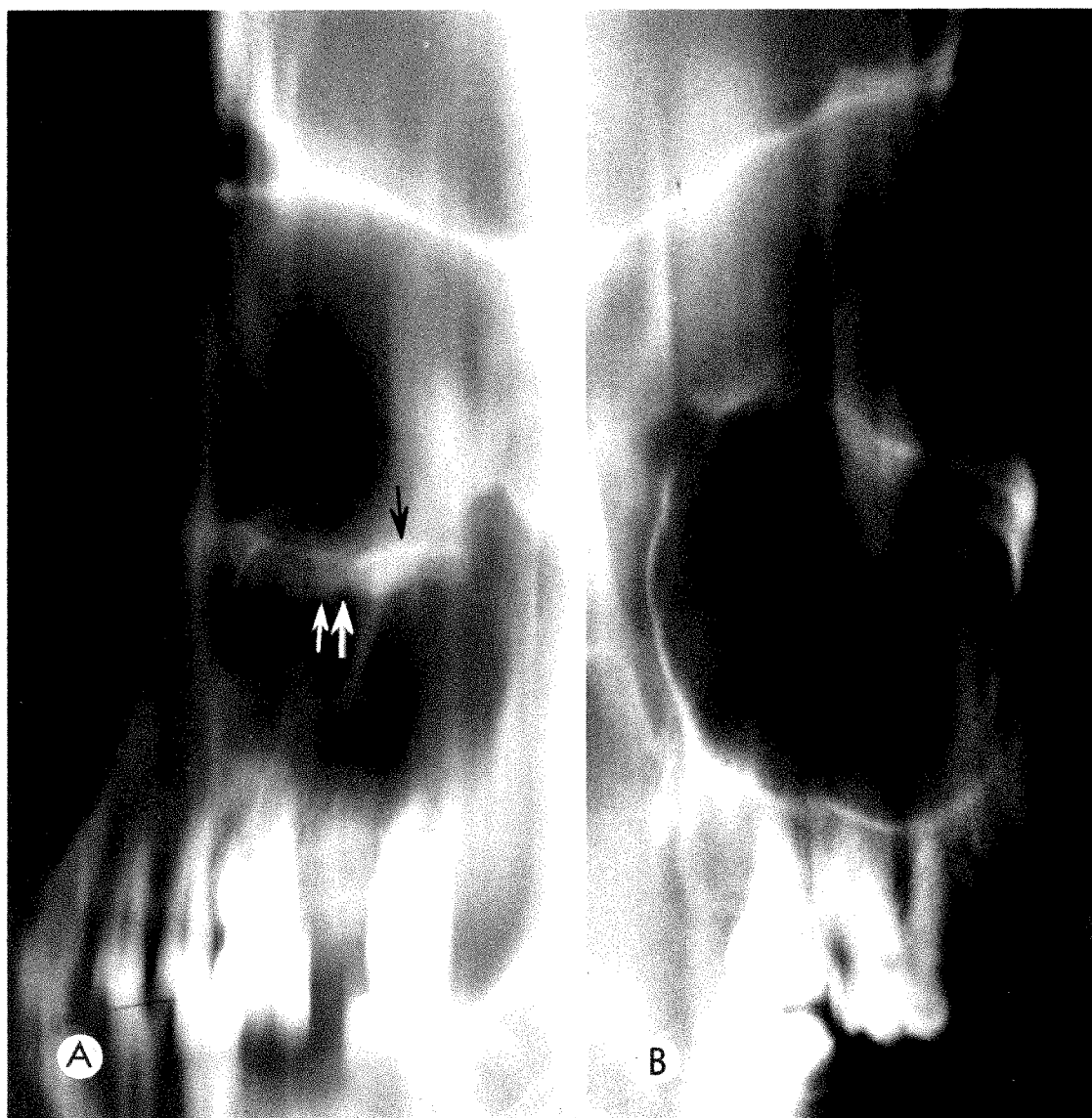


FIG. 3. Patient was kicked in right eye and had diplopia at the limit of upward gaze. Routine roentgenograms showed a fracture of the floor of the orbit. (A) Lateral laminogram showing downward displacement of the floor of the orbit (single arrow) with soft tissue thickening in the roof of the antrum (double arrow). (B) Opposite normal side for comparison.

localized soft tissue mass in the roof of the maxillary sinus.

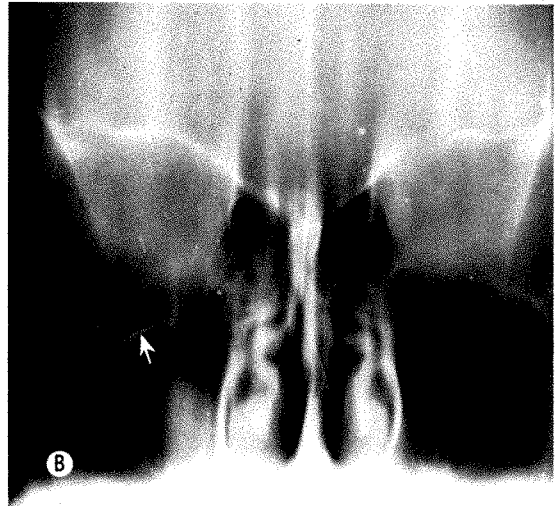
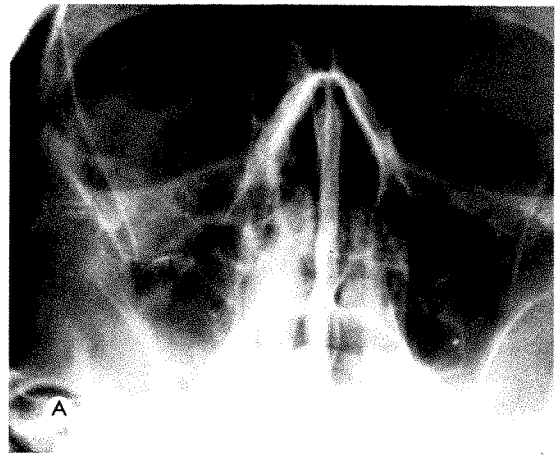
MATERIAL

Twenty-one cases with a definite fracture of at least one orbital wall were studied (Fig. 2 through 6; Table II). One other case had a questionable fracture of the floor of the orbit, both clinically and by laminagraphy, but is not included in this study. Of

these 21 cases, 4 had fractures of both the floor and ethmoid plate, 11 had fractures of the floor alone, 5 had fractures of the ethmoid plate alone, and 1 had a fracture of the roof of the orbit.

The diagnosis of fracture was missed on initial clinical examination in 5 out of 21 cases. Three were floor fractures and 2 were ethmoid fractures. On clinical re-examination of the patient, with knowledge that a

FIG. 4. Another patient who was kicked in the right eye. He had diplopia on upward gaze. (A) Waters' view shows depression of the right orbital floor into the roof of the antrum (arrow). (B) Postero-anterior laminagram confirms the depressed fracture of the right orbital floor (arrow). Mucous membrane thickening is present in the inferior ethmoid, but on the original roentgenograms, the wall appeared intact, so this was not interpreted as a fracture.



fracture was present roentgenographically, the diagnosis was clinically confirmed in 4 of the 5 cases; the 1 case that could not be confirmed was an ethmoid fracture.

Initial routine roentgenographic examination resulted in a missed diagnosis of fracture in 12 of the 21 cases. Five had floor fractures, 5 had ethmoid fractures, and 2 had both areas fractured. Two cases, both of which had fractures of the floor and ethmoid plate, revealed only the presence of the floor fracture on routine roentgenograms. These were not included in the missed diagnosis group. Three of the 12 cases in this missed diagnosis group had orbital emphysema on the routine roent-

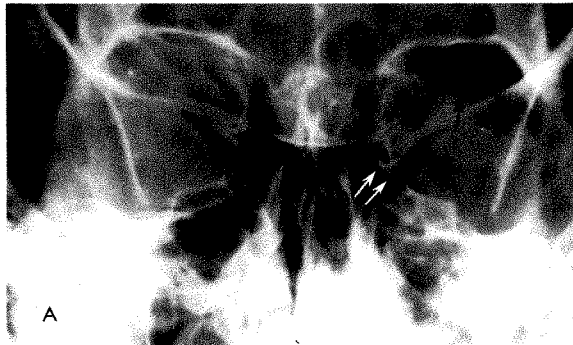


FIG. 5. Patient was kicked in left eye and had diplopia. (A) Posteroanterior roentgenogram shows emphysema in roof of orbit (single arrow) and buckled wall of ethmoid plate (double arrow). (B) Waters' view shows orbital emphysema and depressed fracture of orbital floor with soft tissue mass in roof of antrum (arrow). (C) Posteroanterior laminagram shows both fractures (arrows). Laminagraphy was done after emphysema had been resorbed.

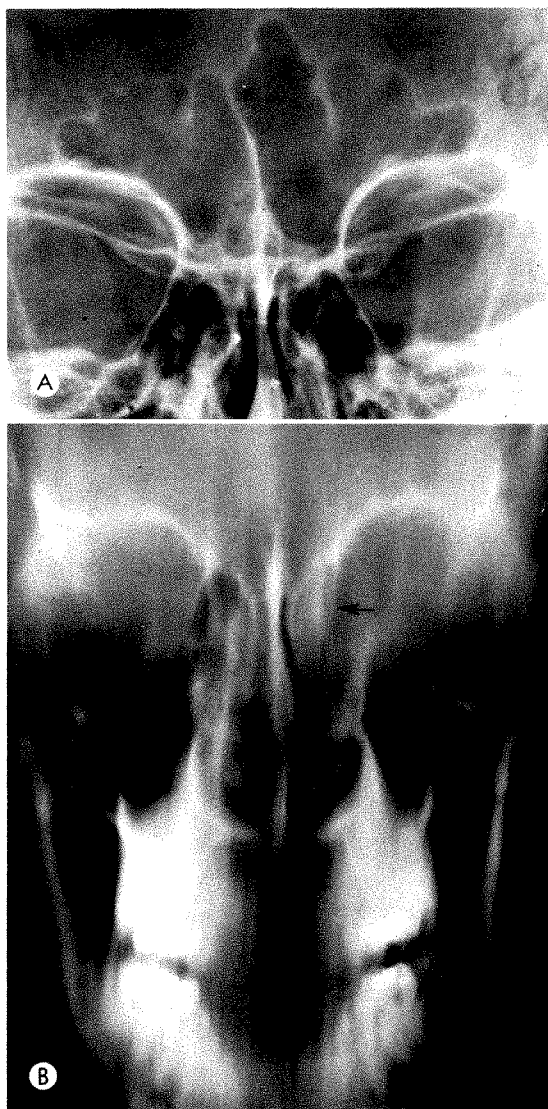


FIG. 6. Another patient who was kicked in the left eye. Physical examination was normal except for tenderness over the inner canthus. (A) Postero-anterior roentgenogram shows no fracture. (B) Posteroanterior laminagram shows opaque left ethmoid with medial displacement of lower portion of ethmoid plate (arrow).

knowledge that a fracture was present, allowed the diagnosis to be made in only 5 of the 12 cases. One of these had a floor fracture, 3 had ethmoid fractures, and 1 had a fracture of both the floor and the ethmoid.

Laminagraphy was performed in 19 of the 21 cases. The diagnosis of fracture was missed only once on laminagrams. In this case, the diagnosis was also missed on routine roentgenograms, and subsequent review of both examinations could not confirm the presence of a fracture. Clinically, this patient had inability to look up and while this could conceivably be due to damage to the inferior oblique muscle without a fracture, this case is included as a missed fracture since this is more likely. This patient has refused exploration.

Orbital emphysema was found on either routine roentgenograms or by laminagraphy in 4 cases. Two of these had ethmoid fractures alone, and 2 had both ethmoid and floor fractures.

genograms. This was evidence that a fracture was present, although the fracture itself was not seen initially. Subsequent review of the missed diagnosis group, with

CONCLUSIONS

Our results indicate that laminagraphy is the most accurate method of diagnosis in internal orbital fractures. It was positive in

TABLE II

	No. of Cases Examined	Initial Positive Diagnosis	Per Cent of Initial Positive Diagnosis	Positive Diagnosis after Second Examination	Per Cent of Positive Diagnosis after Second Examination
Clinical Examination	21	16	76	20	95
Routine Roentgenography	21	9	43	14	67
Laminagraphy	19	18	95	18	95

18 of 19, or 95 per cent, of the cases. Clinical examination was positive initially in 16 of 21 cases, or 76 per cent, although on subsequent clinical re-examination the positive rate was 95 per cent. Routine roentgenographic examination initially was positive in 9 of 21 cases, or 43 per cent, while with a subsequent secondary reading of the roentgenograms, the positive rate was 14 of 21 cases, or 67 per cent.

Routine roentgenograms of the orbit should not be relied upon to exclude an internal orbital fracture.

Howard R. Gould, M.D.
Department of Radiology
St. Vincent's Hospital
153 West 11th Street
New York, New York 10011

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TRAUMATIC ATLANTO-OCCIPITAL DISLOCATION*

WITH CASE REPORT OF A PATIENT WHO SURVIVED

By TRYGVE O. GABRIELSEN and JOHN A. MAXWELL

ANN ARBOR, MICHIGAN

A REVIEW of the literature has not disclosed any previous report of a purely traumatic atlanto-occipital dislocation in a surviving adult. Some pertinent aspects of such an injury will be discussed after presentation of a case.

REPORT OF A CASE*

This 41 year old male was the sole occupant of an automobile which had crashed beside a highway. The details of the accident are unknown because the patient has had persistent amnesia pertaining to the event. After a tracheostomy had been performed in another hospital, he was referred to the University of Michigan Medical Center. The patient has subsequently denied any history of arthritis or previous injury to the head and cervical spine.

Physical examination revealed a conscious but confused man who had an open fracture of the right side of the mandible, massive swelling of the upper posterior part of the neck and suboccipital area, a right lateral rectus palsy, anesthesia in the distribution of the right greater occipital nerve, and sustained clonus of both ankles. No other neurologic abnormalities were found.

Initial roentgenographic examination of the skull and cervical spine revealed only a fracture of the spinous process of the fourth cervical vertebra. Because a more serious cervical spine fracture was suspected, Vinke tongs were inserted, and the patient was placed on a Foster frame. Although only 10 pounds of traction was used for stabilization of the cervical spine, the patient complained bitterly of suboccipital pain after he became more alert.

Repeat roentgenograms of the cervical spine (Fig. 1, *A* and *B*; and 2, *A* and *B*) showed a marked atlanto-occipital dislocation which was definitely not apparent on the initial examination. The cervical traction at this time was reduced to 4 pounds.

* This patient was briefly referred to as Case 1 in an earlier publication.¹⁰

* From the Department of Radiology and Department of Surgery, Section of Neurosurgery, The University of Michigan Medical Center, Ann Arbor, Michigan.

The patient was maintained in gentle skeletal traction for 6 weeks. A neck brace was then applied. At that time, pantopaque myelography was performed. The contrast material was introduced by an uncomplicated lumbar puncture. There was extensive extravasation of pantopaque outside the subarachnoid space at the atlanto-occipital junction (Fig. 3, *A* and *B*).

Bilateral retrograde brachial arteriography was carried out 3 weeks after the injury. The left vertebral artery was normal. The right vertebral artery was considerably smaller than the left one and opacified slowly. It was never visible beyond the fifth cervical vertebra. No abrupt occlusion could be seen. This suggested an obstruction farther distally, presumably at the atlanto-occipital junction.

The patient was discharged to the outpatient clinic 3 months after the accident and instructed to continue wearing the neck brace. Nine months later, the only neurologic abnormality was an anesthesia in the distribution of the right greater occipital nerve. The spinous process of the axis could be palpated 1 cm. to the left of the external occipital protuberance. The patient stated that he always had the sensation of precariously balancing his head on the neck. In spite of this, he had ceased wearing the neck brace, which he again was advised to use.

Multiple follow-up roentgenograms of the cervical spine were obtained, including a submentovertical projection and views during flexion, extension, and lateral bending. Laminagraphy was most helpful. There was suggestion that the previously described avulsion fracture (Fig. 1, *A* and *B*) might be re-united with the anterior arch of the atlas. Although the basion-odontoid relationship appeared to be unremarkable in lateral roentgenograms, the cranium was more displaced to the right with respect to the atlas (Fig. 4, *A* and *B*) than before (Fig. 2, *A* and *B*).

The patient's condition remained essentially unchanged for another 2 months, but he began to complain of a clicking sound on moving his

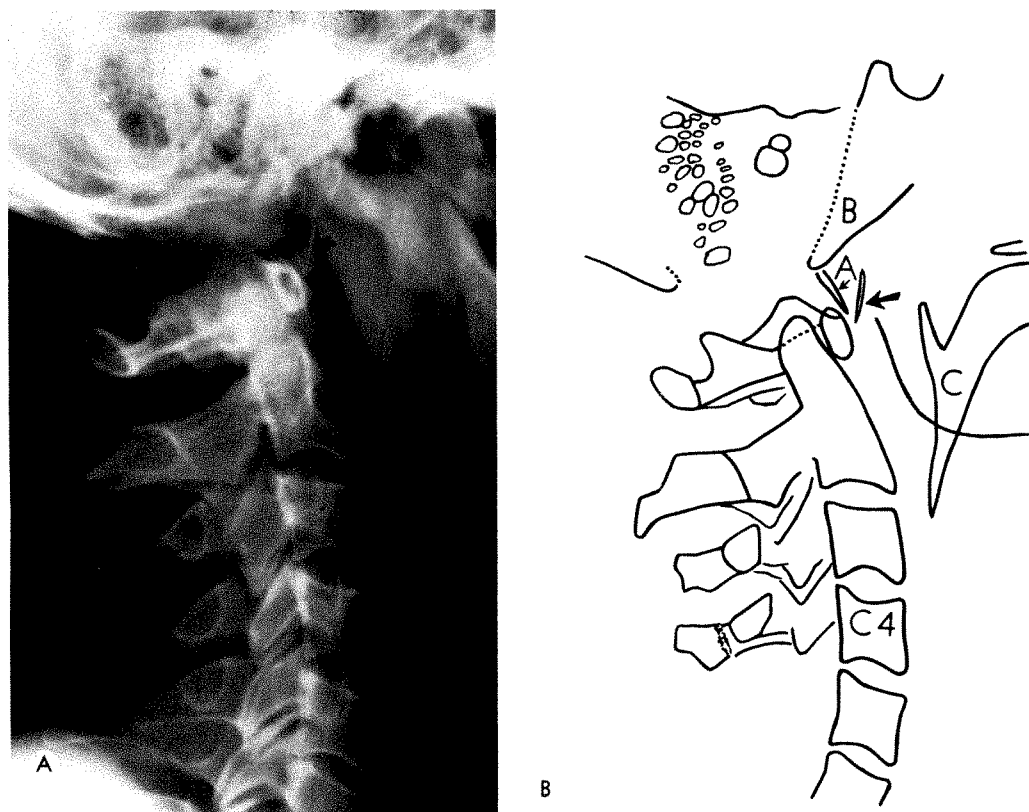


FIG. 1. (A) Lateral roentgenogram of cervical spine made during moderate, unintended rotation of skull and atlas. The barely visible occipital condyles are displaced superiorly and anteriorly with respect to the superior articulating facets of the atlas. (B) Artist's sketch of A, showing basi-occiput of skull dislocated superiorly and anteriorly in relation to ring of atlas. Note position of clivus (B), displaced air in pharynx (C) from prevertebral soft tissue swelling, one of styloid processes (A), and probable avulsion fracture (large arrow). Occipital condyles are not shown in sketch.

head. A craniocervical fusion was accomplished without difficulty about 1 year after the accident. The spinous processes and laminae of the first 2 cervical vertebrae and the posterior portion of the occipital bone were inspected. From this posterior exposure, there was no evidence of fracture or membranous disruption.

DISCUSSION

ANATOMY

The occipito-atlanto-axial joints function together as a unit to provide a ball-in-socket type of motion of the head with respect to the spine.* Significant rotation occurs only at the atlanto-axial articulations, which also permit some degree of flexion-extension movement.^{9,13}

* See article by Martel⁹ for excellent sketches of the occipito-atlanto-axial ligaments.

Most of the flexion-extension motion takes place at the atlanto-occipital joints. Werne¹³ believes that the anteflexion here is limited chiefly by skeletal contact between the basion of the occipital bone and the tip of the odontoid process of the axis via an interposed bursa. He states that extension or retroflexion of the head on the atlas normally is checked by the strong tectorial membrane, which is the cranial extension of the posterior longitudinal ligament of the spine. Skeletal contact between the posterior arch of the atlas and the occipital bone perhaps also limits retroflexion in the atlanto-occipital joints. The superior band of the cruciate ligament is thin and does not participate in any limiting action. The apical ligament is a rather rudimentary structure. It serves no important function.

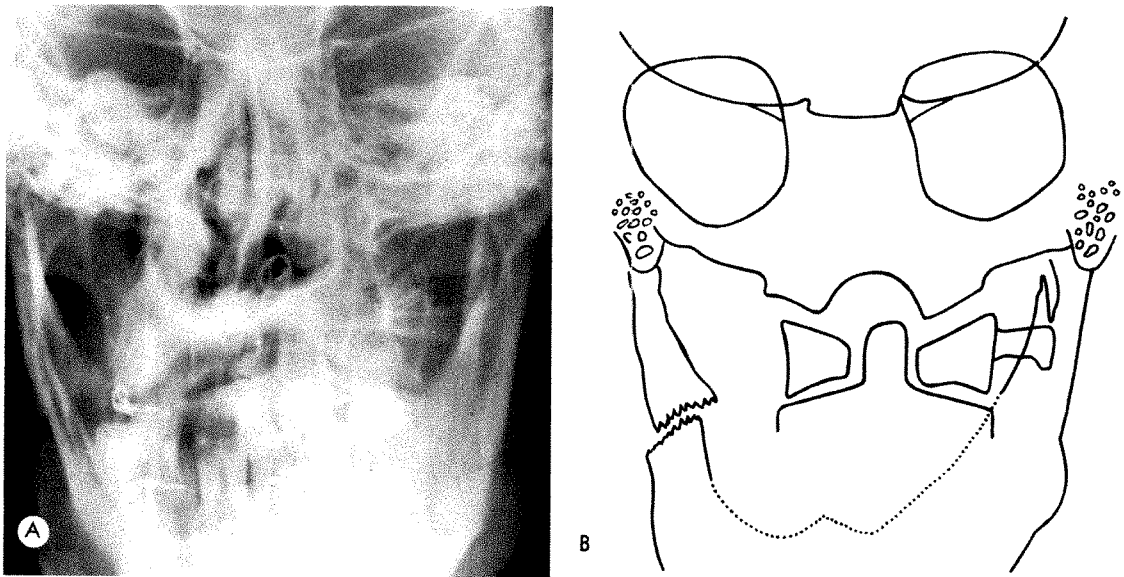


FIG. 2. (A) Slightly rotated anteroposterior view of cranio-spinal junction. (B) Line drawing of A. Joint space between occipital condyles and superior articulating facets of atlas is increased, and cranium is displaced slightly to the right. (Cervical traction reduced since lateral view in Fig. 1.)

The alar ligaments extend from the dorso-lateral borders of the odontoid process of the axis to the medial margins of the occipital condyles. These ligaments not only control rotation of the atlanto-axial joints but also check lateroflexion in the atlanto-occipital joints.¹³

When Werne¹³ removed the tectorial membrane and, in addition, divided the alar ligaments in cadavers, motion at the atlanto-occipital joints was no longer controlled by ligaments. Conditions then provided for dislocation of the skull on the atlas.

MECHANISM OF INJURY

In the absence of any eyewitness account of the accident, statements regarding the mechanism of injury must be speculative. However, there is a definite pattern to the lesions which were sustained.

From the fracture of the right side of the body of the mandible, one may surmise that the skull was probably rotated to the left. The atlanto-occipital dislocation and the associated leakage of pantopaque outside the subarachnoid space anteriorly on the right also suggest that the head was severely hyperextended on the spine and

forced into lateroflexion toward the left. The injured right abducens and greater occipital nerves and the possible occlusion or avulsion of the right vertebral artery lend further support to this hypothesis.

One would not necessarily expect an ordinary atlas fracture to be present. Jefferson⁶ has demonstrated very convincingly that atlas fractures usually result from a blow on the vertex of the skull. The presumed mechanism of injury in our patient is similar to that of judicial hanging with a submental knot, except that in hanging there is relatively little lateroflexion. Persons hanged in this fashion suffer bilateral neural arch fractures of the axis and an anterior dislocation of the body of the axis on the third cervical vertebra.^{11,15} Hanging with a subaural knot fairly consistently produces a fracture of the base of the skull.¹⁵ The mechanical forces responsible for this type of injury also seem to be slightly different from the postulated ones in our patient.

PATHOLOGY

Autopsy information on traumatic atlanto-occipital dislocation is sparse. Kissinger^{7,8} described the pathologic findings

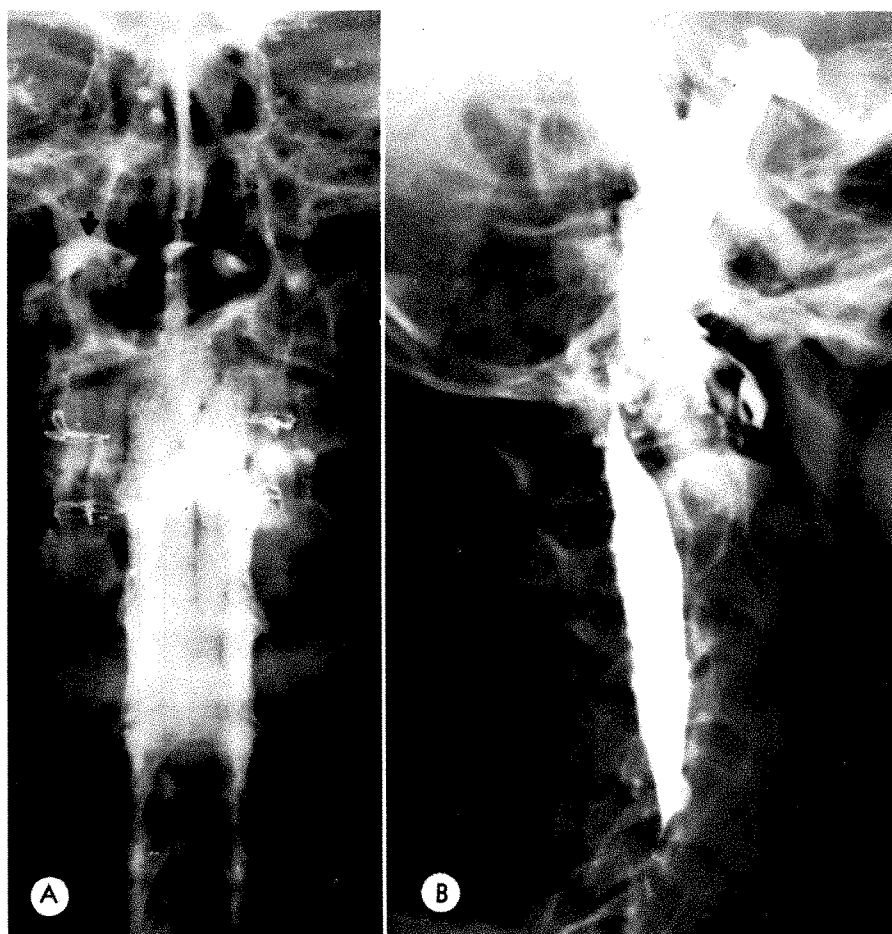


FIG. 3. (A and B) Extensive leakage of pantopaque reveals presence of torn meninges anteriorly and on the right (arrows) at the atlanto-occipital junction. Some contrast material is probably within the synovial joints above and anterior to dens epistropheus. The odontoid-basion distance is now normal.

in 2 such cases in 1899 and 1900. Since the medulla oblongata or the spinomedullary junction had been completely severed, death was instantaneous. As part of his impressive study of the occipito-atlanto-axial articulations, Werne¹³ reviewed autopsy data from a series of fatal cases of fractures and dislocations in this region. Using additional evidence from experiments on cadavers, he concluded that the occipito-atlanto-axial ligaments are extremely strong in the absence of previous disease. He believes that these ligaments are much less apt to rupture than for a fracture to be produced.

In our case of traumatic atlanto-occipital dislocation, there must, at least, have been disruption of the arachnoid membrane, the

dura mater, the tectorial membrane, and the right alar ligament. Whether some of these tears were made possible because of undetected avulsion fractures is open to question. There probably was at least an avulsion fracture from the anterior arch of the atlas (Fig. 1A). Such an avulsion fracture would be equivalent to a rent in the anterior atlanto-occipital membrane. We believe that the lateral atlanto-occipital subluxation resulted from loss of normal checking action by the right alar ligament.

ROENTGENOGRAPHIC FINDINGS

The exact, normal position of the basion with respect to the odontoid process varies slightly, depending on the amount of flexion or extension at the craniospinal junc-

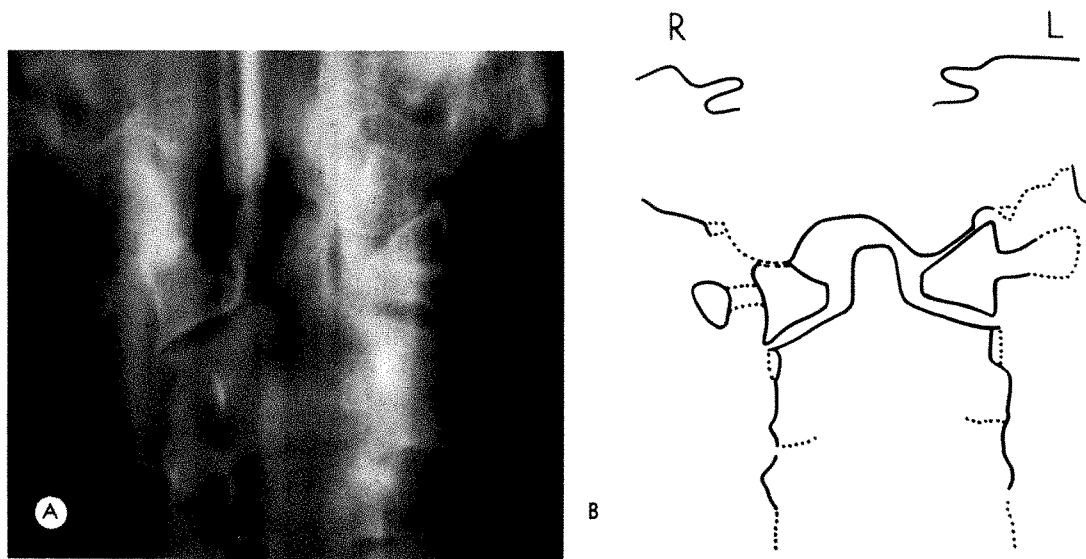


FIG. 4. (A) Anteroposterior laminagram. Lateral displacement of skull to the right with respect to atlas has increased since roentgenogram in Figure 2A was made. Note abnormally narrow left atlanto-occipital joint space. (B) Sketch of A. Right atlanto-occipital joint could never be demonstrated clearly and may not be accurately reproduced in line drawing, which suggests possible erosion or avulsion fracture of right superior facet of atlas. Rotational dislocation may also be present.

tion. During flexion, the basion moves a little forward, and the odontoid-basion distance becomes smaller.¹³ When the head and cervical spine are in neutral position, the tip of the odontoid process is directly beneath the basion and on an average of 5 mm. from it in adults.^{2,14} A distance of up to 1 cm. may be normal in infants and young children, due to incomplete bone growth.¹⁴

All the routine, lateral roentgenograms of the cervical spine in our patient were made at a 60 inch target-film distance and the cassette holder placed next to the shoulder. The odontoid-basion distance initially was 4 mm. It increased to 13 mm. with 10 pounds of skeletal traction and returned to 4 mm. about 6 weeks later.

We believe that the small amount of cervical traction only served to reveal an underlying, traumatic atlanto-occipital dislocation. The vertical translation at the atlanto-occipital articulations was only 0 to 1 mm. when traction was applied to the skull of cadavers. This motion occasionally reached a maximum of 7 mm. after the tectorial membrane had been divided.¹³

The relationship between the occipital

condyles and the superior facets of the atlas is often difficult to see in ordinary anteroposterior roentgenograms but can often be seen on Granger projections. Laminagraphy is very helpful. The atlanto-occipital joint space in our experience normally is about the same size or perhaps slightly smaller than the atlanto-axial joint space.

CLINICAL CONSIDERATIONS

Spontaneous atlanto-axial dislocations occur with relative frequency secondary to inflammatory disease, especially in rheumatoid arthritis and ankylosing spondylitis.^{4,9,12,13} Rare references have been made to similar, nontraumatic displacements at the atlanto-occipital junction.^{3,4,9,12}

Farthing⁵ in 1948 reported a traumatic atlanto-occipital dislocation with survival in a 6 year old child. Unfortunately, the reproductions of the roentgenograms in that case are not very clear. Brocher² wrote in 1955 that he knew of no definitely proven, published account of survival following a traumatic atlanto-occipital dislocation. Blackwood's¹ patient with fractures of the

atlas and axis and atlanto-occipital dislocation succumbed.

Although our patient obviously was subjected to severe trauma, the nervous system escaped surprisingly unharmed. The relatively few neurologic abnormalities and rather unremarkable early roentgenograms of the cervical spine were deceiving and could have created a false sense of security.

Lateral displacement of the spinous process of the axis with respect to the external occipital protuberance is generally due to spontaneous atlanto-axial dislocation.¹⁸ Such malalignment in our case was consistent with the lateral atlanto-occipital dislocation, although some rotary atlanto-axial dislocation may also have been present.

SUMMARY

A case of purely traumatic atlanto-occipital dislocation in a surviving adult has been reported. Rupture of spinal meninges and anterior atlanto-occipital ligamentous structures was demonstrated by roentgenographic studies. A well documented case has apparently not been recorded before. Autopsy reports of traumatic atlanto-occipital dislocation are also rare. The occipito-atlanto-axial ligaments normally are very strong and are not prone to rupture.

Trygve O. Gabrielsen, M.D.
Department of Radiology
University of Michigan Medical Center
Ann Arbor, Michigan

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OBSERVATIONS ON THE SPINE IN MONGOLOIDISM*

By WILLIAM MARTEL, M.D., and JACK M. TISHLER†, M.D.

ANN ARBOR, MICHIGAN

"LOOKING at mongoloid imbeciles is like looking at the stars; the more one looks the more one sees. New things are always appearing and the suggestion is aroused that much more remains hidden from view." —Bleyer,⁶ 1934.

In past years, attention has been called to a number of roentgenologic manifestations of mongoloidism.^{8,13,14,15,16,23} In a recent preliminary publication, atlas dislocation was reported as an incidental finding in 4 of 18 mongoloid individuals, mostly children.²⁶ Review of the literature showed that Spitzer *et al.*,²⁵ in a paper on the skull, teeth and lenses in this condition, briefly mentioned observing "forward displacement of the atlanto-occipital joint" in 9 out of 29 cases but did not give measurements, ages or other details. It was of interest, therefore, to more clearly establish the prevalence of this lesion in mongoloidism and to determine whether there was an age relevance. In the course of this study, it became apparent that asymptomatic, cervical intervertebral disk lesions were often present in young mongoloid adults. These lesions were characterized by narrowing of the disk with associated irregularities of the adjacent end-plates. They had the appearance of Schmorl's nodes and were similar to the lesions in Scheuermann's disease. For this reason the investigation was extended to include the entire spine.

METHOD

Lateral roentgenograms of the cervical spine in flexion and neutral positions were obtained in 70 mongoloid subjects who were largely selected at random. All but 3 of these patients were institutionalized* and

there were 60 males in the group. In addition, anteroposterior and lateral roentgenograms of the dorsolumbar spine were obtained in 31 of the 33 patients who were over 15 years of age. Cine-films and laminagrams of various spinal segments were obtained in 3 patients in whom abnormalities were disclosed. The measurements taken for the atlanto-odontoid distance represent the shortest interval from the base of the odontoid process to the posterior aspect of the anterior arch of the atlas, generally perpendicular to the long axis of the odontoid process. The target-film distance was 60 inches and no correction was made for magnification.

RESULTS

Table I shows the prevalence of atlas dislocation according to 3 arbitrarily chosen

TABLE I
ATLANTO-ODONTOID DISTANCE IN MONGOLISM

Group	Age (yr.)	Normal Limit (mm.)	Distance (mm.)	Cases
I	2-15	5	<4	15
			4	12
			5	4
			6-10	6
			—	37
II	16-37	3	3 or <3	20
			4-5	3
			6-8	4
			—	27
III	42-56	3	3 or <3	5
			9	1
			—	6

* Fifty-nine patients were from The Coldwater State Institution and Training School and 8 were from The Plymouth State Home and Training School.

* Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 28-October 1, 1965.

† Present address: Department of Radiology, Winnipeg General Hospital, Winnipeg, Manitoba, Canada.
From the Department of Radiology, The University of Michigan Medical Center, Ann Arbor, Michigan.

age groups. It should be emphasized that none of the patients were under 2 years of age. Atlas dislocation was present in 14 cases. Six were in the 2-15 year age group, 7 in the 16-37 year age group, and 1 was in the older group which was comprised of only 6 patients. In addition, the arch of C1 appeared somewhat hypoplastic in a number of cases but this was often difficult to evaluate on an absolute basis and its significance was therefore uncertain (Fig. 1). Spina bifida of C1 was observed in 9 cases.

The prevalence of intervertebral disk lesions, both in the cervical and dorsolumbar spinal segments, is summarized in Table II. There was a significant difference between the younger and older individuals. There were only 2 patients in Group I in whom there might have been slight narrowing of an intervertebral disk. In 1 of these

TABLE II
INTERVERTEBRAL DISK ABNORMALITIES
IN MONGOLOIDISM

Group	Age (yr.)	No. of Cases	Reduced Disk	End-Plate Irregularities
<i>Cervical Spine</i>				
I	2-15	37	2 (?)	1 (?)
II	16-37	27	13	12
III	42-56	6	6	4
<i>Dorsolumbar Spine</i>				
II	16-37	26	14	5
III	42-56	5	3	1



FIG. 1. R. Y. 2733. Male, aged 19 years. The atlanto-odontoid distance measured 8 mm. in flexion. The posterior arch of C1 appears somewhat narrow. The end-plate of C2 appears slightly indistinct and there is a suggestion of minimal irregularity anteriorly.



FIG. 2. D. L. 1268. Male, aged 31 years. There is narrowing of the intervertebral disks at C3-4 and C5-6 with erosive-like irregularities of the vertebral end-plates. These have the appearance of Schmorl's nodes. There is anterior marginal bone proliferation, probably secondary to disk prolapse, at these sites.

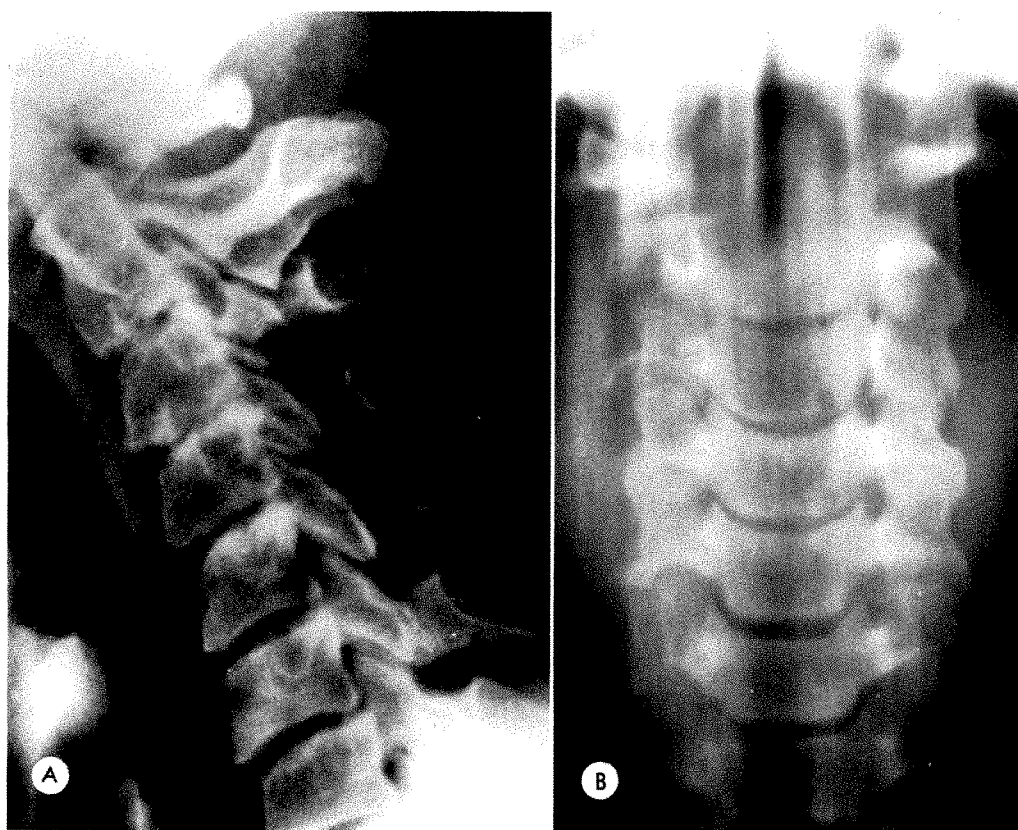


FIG. 3. H. S. 1769. Male, aged 32 years. (A) There is narrowing of almost all of the cervical intervertebral disks with vertebral end-plate irregularities. These are evident anteriorly, particularly at the inferior margin of C2 and C3. The odontoid process is relatively small and conical. (B) Anteroposterior laminagram confirming the presence of vertebral end-plate erosions having the appearance of Schmorl's nodes, seen best here at the inferior aspects of C2, C3 and C4.

individuals, there was also a suggestion of minimal irregularity of the vertebral end-plates at the site in question. However,



FIG. 4. J. S. 661. Male, aged 33 years. There is minimal narrowing of the intervertebral disk anteriorly between C3 and C4 and slight new bone formation along the anterior margin of C3.

definite narrowing of cervical intervertebral disks was observed in 13 patients in Group II (Fig. 2; 3, A and B; and 4). Multiple disks were involved in 9 of these patients and 8 had associated end-plate irregularities. Such irregularities were also observed without associated disk narrowing in 4 additional patients. Thus, there was a total of 17 patients in the 16-37 year age group who had cervical disk narrowing, end-plate irregularities or both. Ten of these patients also had narrowing of one or more intervertebral disks in the dorsolumbar spine and 4 of these had associated irregularities in the adjacent vertebral end-plates (Fig. 5, A, B and C). There were 4 other patients who had similar intervertebral disk lesions in the dorsolumbar spine but in whom the cervical spine was normal. Two of the 7 patients in Group II with atlas dislocation had an

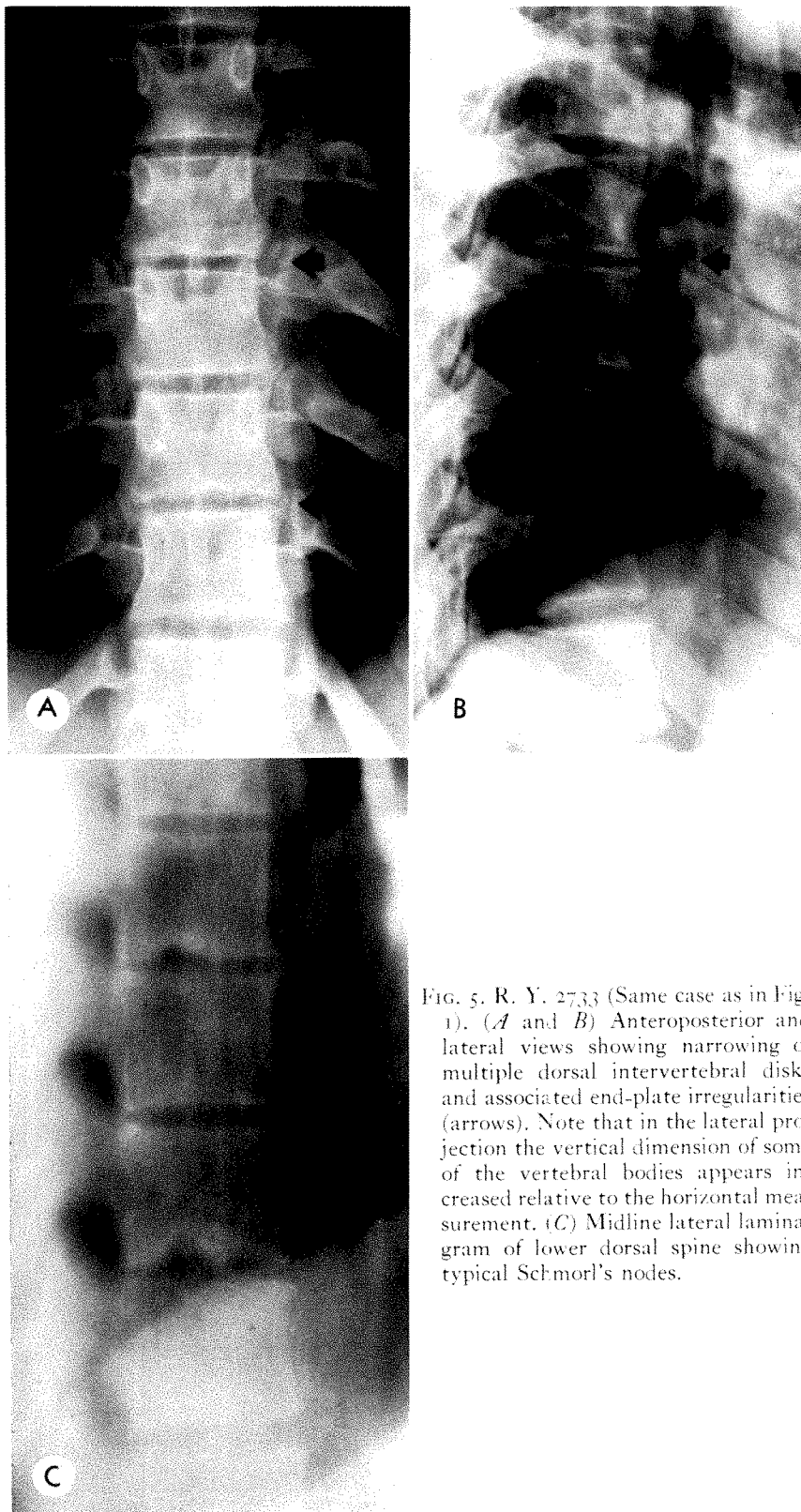


FIG. 5. R. Y. 2733 (Same case as in Fig. 1). (A and B) Anteroposterior and lateral views showing narrowing of multiple dorsal intervertebral disks and associated end-plate irregularities (arrows). Note that in the lateral projection the vertical dimension of some of the vertebral bodies appears increased relative to the horizontal measurement. (C) Midline lateral lamina-gram of lower dorsal spine showing typical Schmorl's nodes.



FIG. 6. H. A. 2234. Male, aged 48 years. There is generalized narrowing of the cervical intervertebral disks with some sclerosis and osteophyte formation. Similar changes were present in the dorsolumbar spine, associated with extensive formation of osteophytes. These are probably the consequence of earlier intervertebral disk lesions associated with Schmorl's nodes.

otherwise normal cervical spine and there were 11 patients with cervical disk lesions who did not have atlas dislocation. All of the 6 patients in Group III had narrowing of one or more cervical intervertebral disks but in 3, ages 48, 53 and 56 years, there were extensive and severe changes of degenerative spondylosis in both the cervical (Fig. 6) and dorsolumbar portions of the spine.

Three of the 31 patients over 15 years of age in whom roentgenograms of the dorsolumbar spine were obtained had spondylolysis of L₅ (Fig. 7). None had a significant degree of spondylolisthesis. One of these 3 patients had intervertebral disk narrowing at the dorsolumbar junction, the second had end-plate irregularities at T₁₀-T₁₂ with anterior wedging of the vertebral bodies

(Fig. 7), and the third had a considerable degree of osteophyte formation in the dorsal region. A fourth patient had spondylolysis of C₄ and an interesting variation in the size of the cervical vertebral bodies (Fig. 8). This consisted of a relative flatness of the bodies of the third and fourth cervical segments. A similar variation, with the bodies of C₃ and C₄ appearing relatively flat, was noted in 2 other patients (Fig. 9). In 2 additional patients, all of the cervical segments appeared relatively flat. The platyspondyly in these 5 patients was not particularly associated with vertebral end-plate irregularities. In 4 additional cases some of the vertebral bodies, particularly in the dorsolumbar spine, appeared relatively increased in their vertical dimension (Fig. 5B). Scoliosis was



FIG. 7. J. K. 3302. Male, aged 16 years. Spondylolysis of L₅ is present. Note anterior wedging of the lower dorsal vertebral bodies. Some of the disks were minimally narrowed in the lower dorsal spine, associated with slight vertebral end-plate irregularities.

observed in 17 of the 31 patients in whom roentgenograms of the entire spine were obtained. It was usually S-shaped, variable in configuration and moderate in degree.

Cine-films in a 10 year old mongoloid female with atlas dislocation confirmed the diagnosis and showed that the abnormal cervical mobility was confined to the atlanto-axial level. Cine-studies of the cervical spine in 2 patients in Group II, both of whom had extensive intervertebral disk abnormalities, disclosed relative immobility of the involved cervical segments. Roentgenograms of the skull, ribs, shoulders, pelvis, hips, hands and wrists, which were obtained in 6 patients in Group II with severe involvement of the intervertebral disks, did not show evidence of a disturbance in skeletal growth or articular cartilage. Furthermore, there was no evidence of previous trauma to the peripheral skeleton.



FIG. 8. D. H. 1480. Male, aged 32 years. There is spondylolysis of C4. Flexion and extension views showed no evidence of fusion of these segments. The upper cervical vertebral bodies appear relatively flat compared with the lower ones. Note a similar appearance in Figure 9.



FIG. 9. M. K. 574. Male, aged 37 years. Early disk narrowing and osteophyte formation. Note the variation in shape of the vertebral bodies and compare with Figure 8. Spina bifida of C1 is present.

Cervical spine roentgenograms in a control group of 25 normal cases between the ages of 16-37 years, matched for age and sex with the cases in Group II, showed no abnormality. The factor of sex was not evaluated.

DISCUSSION

One may postulate that the displacement and increased mobility of the atlas is congenital, possibly due to a malformation or aplasia of the transverse ligament. Whether it occurs in infancy was not evaluated in this study, but it is noteworthy that it was not more common in the older age groups. Atlas dislocation is not important as a diagnostic sign of mongoloidism. Other roentgenologic features^{4,8} are more specific and much more prevalent and, furthermore, it is probably difficult to evaluate this region in infancy when it is particularly important to obtain the diagnosis. The chief reason for calling attention to this finding is that it should not be confused with other conditions associated with displacement of the atlas.

The changes in the disks and adjacent vertebral end-plates are nonspecific. The irregularities of the end-plates are probably the result of herniations of the nucleus pulposus⁵ and, therefore, represent Schmorl's nodes (Fig. 5C). As in Scheuermann's disease, these lesions appear to be conspicuously absent before adolescence. It is noteworthy, however, that unlike that disease, the lesions in mongoloidism are frequent in the cervical spine and anterior wedging of the vertebral bodies, which is frequent in Scheuermann's disease, was only occasionally notable in these patients (Fig. 7).

The pathogenesis of these lesions, as in Scheuermann's disease, is not known. Trauma may have an important role, particularly inasmuch as these are largely institutionalized patients and joint laxity is characteristic in this condition. However, mongoloid individuals tend to be placid, not likely to engage in much muscular activity, and, furthermore, the joint laxity tends to disappear in the older child.²⁰ Nevertheless, the trauma may be of an endogenous nature, due to faulty musculoskeletal development, and in this connection the frequent finding of scoliosis is noteworthy. The early appearance of severe degenerative spondylosis in these individuals (Fig. 6 and 9) may be related to these intervertebral disk lesions themselves²⁷ or to the postulated factor of endogenous trauma. In considering the role of trauma, the occurrence of spondylolysis in some of these individuals is of interest. It is generally believed that the defect in this condition is usually a stress fracture. However, its familial occurrence suggests that it evolves as a result of an inherited, developmental weakness in the pars interarticularis, causing an unusual stress at this site.²⁸ One may postulate that mongoloid persons frequently have such a congenital weakness and that superimposed endogenous trauma on a long term basis produces spondylolysis. However, the relatively small number of patients in this series in whom lumbar spine roentgenograms were obtained probably does not justify a

definite conclusion as to whether spondylolysis is significantly common in mongoloidism.

The conspicuous absence of the intervertebral disk lesions in childhood, their tendency to be multiple and not associated with gross fractures and the lack of traumatic lesions in the peripheral bones and joints indicate that trauma may not be the only factor in their pathogenesis. It is possible that there is an intrinsic defect in the cartilage plates of the intervertebral disks, allowing herniations of the nucleus pulposus in the face of minimal trauma. Possibly the defect is in the nucleus pulposus causing it to expand unduly. It is tempting to speculate on the possibility of an abnormality of the mucopolysaccharides, either of the cartilage or nucleus pulposus. It is well known that ocular lesions, including corneal and lenticular opacities and keratoconus, are significantly frequent in mongoloidism early in life.^{10,11,20} Such lesions also occur in other hereditary connective tissue diseases, some of which are known to be associated with mucopolysaccharide abnormalities.⁷ For this reason the urinary acid mucopolysaccharides were examined in 3 of our cases in whom there was severe cervical involvement. The 24 hour urine specimens contained normal amounts of acid mucopolysaccharides and tentative qualitative analysis by paper chromatography likewise showed no abnormality. These results, by no means, exclude the possibility of abnormal tissue mucopolysaccharides. It would be of interest to learn whether ocular complications are more common in those patients who have these vertebral lesions.

There have been recent indications that there may be a metabolic abnormality associated with mongoloidism. The serum uric acid levels have been reported to be significantly elevated¹² and there appears to be a sensitivity to pyridoxine deficiency.¹⁹ A significant number of these individuals show a characteristic lacrimal protein pattern which is not generally found in other subjects² and there appear to be significant differences in the plasma proteins as well.^{3,21}

These biochemical findings are of interest, but it remains to be determined whether they are related to the vertebral lesions under discussion.

Other theories of pathogenesis deserve comment, particularly that of Cloward and Bucy⁹ who called attention to the frequent occurrence of Scheuermann-like lesions in patients with spinal extradural cysts. They suggested that the cysts caused venous congestion and stasis in the involved vertebral bodies and this was responsible for the end-plate irregularities. Presumably chronic hyperemia weakened the bone structure sufficiently so that herniations of the nucleus pulposus then occurred. One might postulate that vertebral venous stasis, whatever the etiology, might be the basis for these lesions. Experimental support for this theory of venous stasis was recently presented.¹⁷

It is of interest that irregularities of the dorsal vertebral end-plates and scoliosis have been described in Turner's syndrome.^{1,4,18,22} Similar vertebral lesions associated with platyspondyly are known to occur in various bone dysplasias.²⁴ Whether there is indeed a common denominator, such as vertebral venous stasis, to account for these lesions in all of these conditions or whether various pathogenetic factors are responsible remains to be determined.

SUMMARY

Atlas dislocation was observed in 14 of 70 mongoloid individuals of various ages. In addition, Scheuermann-like lesions, probably representing Schmorl's nodes, were present in young adults in the cervical and dorsolumbar segments of the spine. These were conspicuously absent in childhood. Possible pathogenetic factors are discussed.

William Martel, M.D.
Department of Radiology
University Hospital
Ann Arbor, Michigan

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CONGENITAL ABSENCE OF A PEDICLE IN THE CERVICAL SPINE*

By CHARLES B. WILSON, M.D., and HORACE A. NORRELL, JR., M.D.

LEXINGTON, KENTUCKY

AN ENLARGED intervertebral foramen is a roentgenographic finding with high diagnostic value in a patient suspected of harboring a spinal cord tumor. The incidental discovery of an enlarged intervertebral foramen during the course of roentgenographic examination may not be indicative of a dumbbell spinal tumor and, in fact, may be unrelated to the patient's problem. Six cases have been reported in which an enlarged intervertebral foramen was the result of congenital absence of a pedicle in the cervical spine. The purposes of the authors are to report 2 additional cases of this unusual spinal anomaly and to consider the roentgenographic features which distinguish it from enlarged intervertebral foramina due to other causes.

REVIEW OF PREVIOUS CASES

Hadley published a paper in 1946 under the title, "Congenital absence of pedicle from cervical vertebra."⁴ Three cases were included in this report. Case 1 was a typical example of congenital absence of a pedicle but the second and third cases were not. Roentgenograms of Case 2 showed a concave depression of the posterolateral surface of the vertebral body and normal articulations of the affected vertebra with the corresponding articular facets of the adjacent vertebrae. The third cervical vertebra was involved in his third case. The entire lateral mass was absent on one side and C2 articulated with C4 on that side. The axis was asymmetric as were the atlanto-axial articulations. The posterolateral surface of the C3 vertebral body was concave on the abnormal side. Hadley⁵ later accepted the second and third cases as examples of destructive bone changes pro-

duced by a tortuous vertebral artery, leaving Case 1 as the only example of congenital absence of a pedicle. This patient was examined following trauma to the neck and the pedicle of the fifth cervical vertebra was absent on the left.

The second case was reported by Steinbach, Boldrey and Sooy⁸ in 1952. Absence of the right pedicle of the seventh cervical vertebra was an incidental finding during examination for a swallowed foreign body. Surgical exploration did not disclose the expected tumor at this level. Subsequent myelography confirmed the operative finding of an anomalous dural pouch transmitting both the C7 and the C8 nerve roots.

Buetti² reported the third case in 1953. Absence of the left pedicle of the fifth cervical vertebra was found during the course of studies in a patient suspected of harboring a tumor of the posterior fossa. The fourth case was reported in 1958 by Abel¹ as an incidental finding in a patient who had sustained an injury of the cervical spine. The left pedicle of the sixth cervical vertebra was absent. Flexion and extension roentgenograms in an oblique projection showed wide separation of the anomalous posterior articulations between the fifth and sixth cervical vertebrae during flexion, suggesting that this was not a true joint.⁹

Zatz, Burgess and Hanbery⁹ reported the fifth and sixth cases in 1963. One patient had symptoms suggesting a lesion of the cervical cord. The right pedicle of the sixth cervical vertebra was absent. No intraspinal abnormality was found by myelography but the C6 and C7 nerve roots shared a common dural pouch. Their second patient was investigated following a neck injury. The left pedicle of the fifth

* From the Department of Surgery, Division of Neurosurgery, University of Kentucky School of Medicine, Lexington, Kentucky. Supported in part by the Fred A. Rankin Fund for Surgical Research.



FIG. 1. Case 1. Lateral roentgenogram of cervical spine. The laminae of C₄ do not unite at the midline. The joint space of the posterior articulation between C₄ and C₅ is not seen clearly because of the large and malformed lateral mass on the right side.

cervical vertebra was absent and a dural pouch common to the C₅ and C₆ nerve roots was shown by myelography.

Buetti² referred to a case described in 1869 by Gruber. This case does not have roentgenographic confirmation. Holt and Hodges⁶ referred to asymmetric enlargement of the intervertebral foramina in association with developmental localized enlargement of the cervical spinal canal but made no mention of an absent pedicle.

REPORT OF CASES

CASE 1. A 28 year old secretary was admitted to the Presbyterian Hospital in New York for evaluation of complaints referable to her head, neck and right upper extremity. She was seen in neurosurgical consultation on November 27,

1962 by Dr. James W. Correll at the request of Dr. Robin W. Rankow.

Pain had been present in the right posterior cervical and occipital regions for 3 years, becoming more severe in the 2 months preceding hospitalization. During the previous month, the pain had been associated with the feelings of numbness and heaviness in the right upper extremity and a feeling of numbness in both feet. Writing became difficult and the character of her handwriting changed. Examination revealed slight weakness of the right triceps muscle and limitations of movement of the cervical spine, greatest on turning the head to the right. Roentgenograms of the cervical spine were interpreted as showing a congenital malformation of the C₄ vertebra, consisting of an absence of the right pedicle, a prominent transverse process, a large intervertebral foramen between C₃ and C₄ and spina bifida of C₄ (Fig. 1, 2 and 3). A myelogram made on November 28, demonstrated a common dural pouch for the C₄ and C₅ nerve roots on the right with a smooth concave extradural filling defect above the anomalous root shadow (Fig.



FIG. 2. Case 1. Anteroposterior roentgenogram of the cervical spine. Spina bifida and an elongated right transverse process are noted on the C₄ vertebra. The relationships of the articular facets of C₃, C₄ and C₅ are abnormal.

4). No treatment was advised and the patient was discharged from the hospital on November 29, 1962.

In January, 1963, sharp pain in the right occipital region occurred daily followed by dull aching pain in the same area. A month later she was no longer able to rotate her head to the right and attempts to do this precipitated the pain. The patient was admitted to the Charity Hospital of Louisiana in New Orleans for further studies on April 23, 1963. Examination at that time confirmed limitation of head rotation to the right, and, at rest, the head was held cocked to the right. The right shoulder drooped slightly and the neck was foreshortened with slight webbing. The right trapezius muscle bulk was decreased. Generalized hyporeflexia, absent abdominal skin reflexes and equivocal Babinski reflexes bilaterally were notable.



FIG. 3. Case 1. Right anterior oblique roentgenogram of the cervical spine. There is a large intervertebral foramen between C₃ and C₅. The right lateral mass of C₄ is bulbous and the superior and inferior articular surfaces are malformed. The right pedicle of C₄ is missing while the pedicles above and below this level are relatively small and large, respectively.



FIG. 4. Case 1. Frontal cervical myelogram. A single dural pouch transmits the C₅ and C₆ nerve roots on the right side. This common dural pouch is midway between the pouches for the C₅ and C₆ nerve roots on the left. The C₆ nerve roots entering the lower portion of this dural pouch pass in a direct lateral direction in contrast to the downward course of corresponding roots on the left side. The dural pouch which transmits the C₇ nerve roots is larger on the right than on the left because a small number of C₆ roots join those of C₇. The concave indentation of the dural sac immediately above the common dural pouch is caused by the large lateral mass of C₄.

Sensory examination was normal except for decreased perception of pin prick in the right supraclavicular fossa and right index finger.

An abnormality in the region of the foramen magnum was suspected clinically but lamina-grams taken through the craniovertebral junc-



FIG. 5. Case II. Lateral roentgenogram of the cervical spine taken in a position of forward flexion. A radiolucent area is seen in the region normally occupied by the pedicles and lateral masses of C6. The laminae of C5 and C6 are fused.

tion were normal. A lumbar puncture was normal including the Queckenstedt test in various positions of the neck. A pneumoencephalogram was normal.

Surgical exploration was undertaken on May 21, 1963 to visualize the anomalous nerve roots and the high cervical region. The neural arch of C4 was bifid, the right lamina lying slightly above the left lamina. The right lamina was unstable as a result of excessive movement at its lateral articulations with the C3 and C5 vertebrae. The large bulbous lateral extremity of this lamina (lateral mass) lay dorsal to the

inferior articular process of C3. The dural sac was exposed by a laminectomy of C1 to C5. The dural sac was displaced medially by the lateral mass of C4, and the common dural investment of the C4 and C5 nerve roots appeared stretched around its inferior surface. The intraspinal portion of this bony mass was removed. Intradural inspection confirmed passage of the right C4 and C5 nerve roots into a common dural pouch. The right C2 and C3 posterior nerve roots were divided. No other abnormality was disclosed.

The patient reported in July, 1963 that she was free of headaches but that slight numbness of the feet and right hand persisted.

CASE II. An 18 year old male was admitted to the University of Kentucky Hospital on August 11, 1964 following an automobile accident. He had sustained multiple fractures of the facial bones and mandible. Neurosurgical consultation was requested because of cerebrospinal rhinorrhea and a suspected injury of the cervical spine.

Roentgenograms of the cervical spine showed

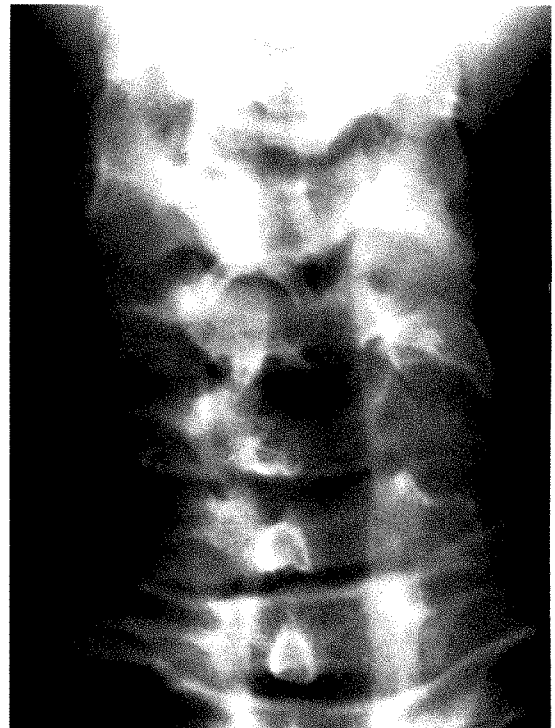


FIG. 6. Case II. Anteroposterior view of the cervical spine. A bulbous lateral mass of C6 is seen on the left side.

straightening of the cervical curvature and an abnormality in the region of C6. Although a tracheostomy had been performed rendering examination more difficult, the patient's neck was held rigidly. Any movement of the neck was painful, and, when rising to a sitting position, he lifted his head with one hand placed beneath the occiput. Roentgenograms taken on August 18, 1964 showed an absence of the C6



FIG. 7. Case 11. Left anterior oblique roentgenogram of the cervical spine. The pedicle of C6 is absent on the left side. The articular mass of C6 is large and is displaced dorsally relative to the articular facets of C5 and C7.



FIG. 8. Case 11. Lateral laminagram of the cervical spine. This cut was made to the left of midline. A bony bar joins the laminae of C5 and C6.

pedicle with a wide intervertebral space between C5 and C7. The laminae of C5 and C6 were fused on the left by a narrow bony bar (Fig. 5, 6 and 7). Laminagrams confirmed an absence of the left C6 pedicle and fusion of the laminae of C5 and C6 (Fig. 8).

A cervical myelogram was interpreted as normal. The patient complained of minimal discomfort in the neck at the time of discharge on August 28, 1964. He was free of symptoms

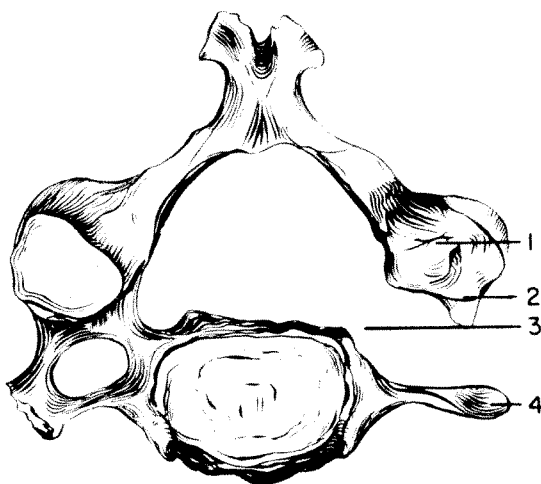


FIG. 9. Diagram illustrating superior surface of a cervical vertebra with congenital absence of a pedicle. 1—absent superior articular facet; 2—malformed lateral mass; 3—absent pedicle; 4—abnormal transverse process.

and had a full range of painless motion when last seen as an outpatient on October 6, 1964.

ROENTGENOGRAPHIC DIAGNOSIS

The critical projection for the roentgenographic demonstration of absence of a pedicle is a 45° anterior oblique view of the involved side (Fig. 9 and 10). This anomaly may be suspected on the basis of frontal and lateral studies but the oblique view is essential to the diagnosis. The following features are characteristic:

1. The *pedicle* of the involved vertebra is lacking entirely. The superjacent and subjacent pedicles have a normal shape, although they may be slightly larger or smaller than contralateral pedicles of the corresponding vertebrae.

2. The *intervertebral foramen* is elongated in the axis of the spine, extending from the pedicle above to the pedicle below the involved vertebra. The dorsoventral diameter of the foramen is increased as a consequence of the dorsally displaced lateral mass.

3. The *lateral mass* of the involved vertebra is malformed and occupies a position dorsal to a line joining the lateral masses of the other cervical vertebrae. The inferior articular facet is dorsal to the superior

articular facet of the subjacent vertebra. The superior articular facet is absent as such and the superior tip of the malformed lateral mass lies upon the dorsal surface of the superjacent lamina and inferior articular facet. The space between these latter structures widens in the position of forward flexion, indicating the unstable relationship which exists at this point.⁹

4. The *transverse process*, seen also in the opposite anterior oblique projection, is deficient in its dorsal portion. Associated abnormalities of the transverse process may be present, e.g., downward angulation or excessive length.

5. The dorsolateral surface of the affected *vertebral body* is perfectly straight as if the



FIG. 10. Diagram of congenital absence of a pedicle (45° oblique view). 1—abnormal transverse process; 2—absent articular facet; 3—dorsally displaced and malformed lateral mass.

pedicle had been carefully removed at its base. The dorsolateral surfaces of the 2 vertebral bodies bordering the large intervertebral foramen are also straight.

6. The opposite lateral mass and its articulations are normal. Each of the 2 cases herein reported had an associated anomaly. The laminae of the fourth cervical vertebra failed to fuse in Case I, an uncommon site for spina bifida occulta. The left laminae of the fifth and sixth cervical vertebrae were fused by a narrow bony bar in Case II.

DIFFERENTIAL DIAGNOSIS

Dumbbell spinal tumors are the most frequent cause of an enlarged intervertebral foramen.³ The foramen is enlarged by an isthmus joining intra- and extraspinal components of a tumor, the majority being neurofibromas. Although primary and metastatic tumors of the vertebral column may cause enlargement of an intervertebral foramen, the nature of the process can be suspected on the basis of associated roentgenographic findings. Four of the 8 reported cases of congenitally absent pedicle were initially thought to represent dumbbell spinal tumors which, therefore, represent the greatest problem in differential diagnosis.

In 1958 Hadley⁵ reported another cause of an enlarged intervertebral foramen in the cervical spine. He described destructive bone changes caused by tortuosity of the vertebral artery. Slover and Kiley reported an additional case of an enlarged intervertebral foramen caused by a tortuous vertebral artery with angiographic verification.⁷ This deficit is illustrated in Figure 11.

Table 1 contains the important roentgenographic features of the 3 benign conditions—congenital absence of a pedicle, dumbbell spinal tumor and tortuosity of the vertebral artery—which may cause enlargement of an intervertebral foramen in the cervical spine.

DISCUSSION

Congenital absence of a pedicle has heretofore been considered an asymptomatic

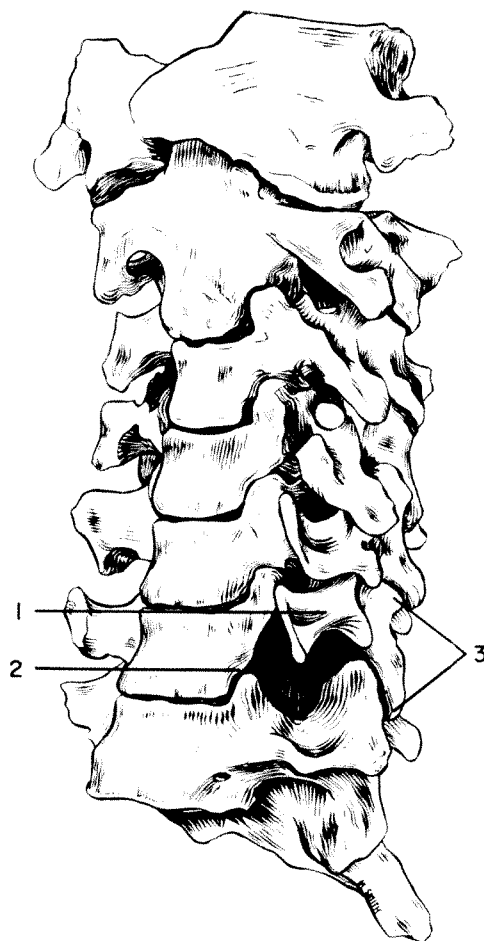


FIG. 11. Diagram illustrating vertebral erosion secondary to a tortuous vertebral artery (45° oblique view). 1—normal transverse process; 2—concave eroded body; 3—normal articular facets.

roentgenographic curiosity. However, the spinal instability associated with this anomaly may predispose to soft tissue injuries following trauma to the cervical spine.

Case I of the present report had signs and symptoms indicating involvement of cervical nerve roots and the spinal cord. Despite the fact that the lateral mass occupied a dorsal position relative to the floor of the spinal canal, the common dural pouch for the C5 and C6 nerve roots was stretched around the lower edge of the bulbous lateral mass. Improvement followed surgical correction of this abnormal anatomic relationship, but this must be regarded with a degree of skepticism. The case bears a re-

TABLE I
DIFFERENTIATING FEATURES OF CONDITIONS ASSOCIATED WITH ENLARGED INTERVERTEBRAL FORAMEN

	Absent Pedicle	Dumbbell Tumor	Tortuous Vertebral Artery
Pedicle	absent	present; adjacent pedicles are thinned along the surface bordering the enlarged foramen	may be absent or thinned to a variable degree
Shape of enlarged foramen	ovoid	round	irregular due to extension into vertebral body
Lateral mass	dorsal position without destruction of ventral surface; malformed	ventral surface is eroded	normal
Articular facets	superior articular facet absent; ventral surface of lateral mass rests on dorsal surface of lamina and inferior facet of superjacent vertebra	normal	normal
Transverse process	malformed	normal (may be thinned)	normal (may be thinned)
Vertebral body	normal	dorsal concavity of adjacent vertebrae	dorsal concavity which may extend deeply; sclerotic border is characteristic
Contralateral pedicle	normal	medial aspect may be destroyed by intraspinal tumor	normal
Multiple vertebral levels involved	no	yes, in some patients with multiple neurofibromatosis	has been reported
Levels of involvement	C4-C7	C2-C7	C2-C6
Myelography	single dural pouch for adjacent nerve roots transmitted through the large foramen	diagnostic of intraspinal tumor	normal
Vertebral angiography	normal	may show slight deflection away from the large foramen	diagnostic; tortuous artery conforms to size and shape of large foramen
Paraspinous mass	no	may be present	no

semblance to Case 1 of Zatz *et al.*,⁹ in which the neurologic manifestations were not attributed to the spinal anomaly. The matter of symptoms arising spontaneously with this anomaly remains an open issue.

Myelography is diagnostic but should seldom be required. The study was reportedly normal in our second patient but globulation of the contrast medium prevented adequate visualization of the cervical nerve

root pouches. A dural pouch common to 2 nerve roots at the affected level was demonstrated in 4 other cases^{8,9} and almost certainly was present in this case as well.

Age of the patient is of no value in arriving at a diagnosis. Dumbbell tumors occur at all ages and 3 of Hadley's patients with bone changes produced by a tortuous vertebral artery were less than 36 years of age. This latter fact suggests that tortuosity of the vertebral artery may have a development basis in certain cases, although it has been considered as an acquired condition in the present paper. Degenerative changes in the vertebral arteries were found in the 4 postmortem studies reported by Hadley.

The reader is referred to Hadley's paper for a lucid description of vertebral changes produced by a tortuous vertebral artery.⁶

SUMMARY

Congenital absence of a pedicle in the cervical spine results in a large intervertebral foramen which may be confused with 2 acquired conditions: a dumbbell spinal tumor and vertebral erosion produced by a tortuous vertebral artery. Two cases with this developmental defect are added to the 6 reported previously. The roentgenographic features of this congenital disorder

and its differentiation from the two acquired conditions are discussed.

Charles B. Wilson, M.D.
Division of Neurosurgery
University of Kentucky Medical Center
Lexington, Kentucky 40506

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COMPARISON OF GAS AND POSITIVE CONTRAST IN EVALUATION OF CERVICAL SPONDYLOSIS*

By GABRIEL WILSON, M.D.,† WILLIAM WEIDNER, M.D.,‡ and
WILLIAM HANAFEE, M.D.§
LOS ANGELES, CALIFORNIA

CERVICAL spondylosis is the most frequent cause of spinal cord or nerve root deficits in elderly people. Myelography is often employed in this problem to ascertain cord or nerve root compression.

HISTORY

In 1918, Dandy⁸ proposed the use of air for the study of the spinal subarachnoid space following ventriculography. The use of air was practically abandoned following the introduction of lipiodol in 1922.⁹ Young and Scott,¹² in 1938, began using air via the lumbar and cisternal route in myelography. Lindgren^{6,7} introduced suboccipital air myelography in Sweden in 1939; and between 1939 and 1948, in a series of approximately 2,000 examinations, he used oil in only 26 cases. His objections to the use of oil were based upon lipiodol. In 1944, pantopaque was introduced by Steinhausen and his associates.¹⁰ Although not the ideal myelography medium, pantopaque has proven since its introduction to be the best positive contrast medium available.

Roth⁸ developed the technique of gas myelography by positive pressure injection via the lumbar route. At the Seventh Symposium Neuroradiologicum in 1964, Feria and Radberg⁴ described their method of gas myelography by positive pressure injection via the lumbar route using a laminographic unit with tilting table. We have combined this method with pantopaque myelography for the evaluation of cervical spondylosis.

TECHNIQUE OF EXAMINATION

The patient is placed on the roentgenographic table in the prone position. A small pillow or folded sheet is placed under the abdomen to lessen the normal lumbar lordosis. After sterile preparation, a skin wheal is raised with 1 per cent xylocaine just caudal to the spinous process of the third lumbar vertebra. The table is tilted so that the patient is upright standing at about a 45 degree angle. A No. 18 gauge short bevel 3½ inch spinal needle is inserted and directed precisely into the midline under fluoroscopic control. If at all possible, only one pass should be made at the subarachnoid space because multiple punctures may cause a leak of cerebrospinal fluid into the potential space between arachnoid and dura with an increased incidence of extradural or extra-arachnoid deposition of pantopaque.

After successful lumbar puncture has been accomplished, the spinal fluid manometrics are recorded. Normal manometrics are confirmation of the satisfactory position of the needle tip in the subarachnoid space. However, a large portion of the spondylotic patients may have a partial block.

If the spinal fluid is bloody, it is not advisable to inject the pantopaque. The incidence of arachnoiditis is increased in the presence of a bloody tap.⁵ Following manometrics, a rubber tubing 10 inches long is connected to the needle and 0.5 cc. of pantopaque is injected into the subarachnoid space under constant fluoroscopic ob-

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† Assistant Professor (in Residence at Harbor General Hospital), Department of Radiology, University of California at Los Angeles Center for the Health Sciences, Los Angeles, California.

‡ Associate Professor, Department of Radiology, University of California at Los Angeles Center for the Health Sciences, Los Angeles, California. Chief Radiologist, Harbor General Hospital, Torrance, California.

§ Associate Professor, Department of Radiology, University of California at Los Angeles Center for the Health Sciences, Los Angeles, California.

servation. The pantopaque should fall away promptly from the tip of the needle and drop into the caudal sac. The remainder of the pantopaque is then injected. Twelve cubic centimeters of pantopaque is used for lumbar myelography and 18 cc. for cervical or thoracic myelography. The stylet is replaced in the needle and the patient's back is covered with a sterile drape sheet which is taped in place.

Routine roentgenograms include postero-anterior, oblique and translateral views of the lumbar as well as the cervical areas.

Under fluoroscopic control, the pantopaque is removed and the needle left in place.

The patient is transferred to a tilting laminagraphic table and placed on his left side in a 30 to 40 degree Trendelenburg position. The head and lumbar spine are carefully supported with padding to assure horizontal alignment of the entire spine. If lateral bending occurs, the laminagraphic cuts will be oblique across the spinal canal and the definition of the cord will be unsharp.

Cerebrospinal fluid is allowed to drip freely from the lumbar puncture needle which is still in place. The total volume of cerebrospinal fluid in the spinal portion of the subarachnoid space in normal persons varies from 50 to 75 cc.¹ The amount obtained in this procedure is usually between 45 and 50 cc. After the flow of cerebrospinal fluid ceases, the lumbar puncture needle is then connected to a manometer through an open three way stopcock (Fig. 1). Oxygen is introduced into the spinal subarachnoid space until the intrathecal pressure is maintained between 300 and 500 mm. of water. The elevated intrathecal pressure increases the resorption of cerebrospinal fluid which allows complete gas filling of the spinal subarachnoid space.

The patient frequently complains of paresthesias in the shoulders and upper extremities as the intraspinal pressure is elevated. This is a rough guide to the oxygen-cerebrospinal fluid level in the spinal canal.



FIG. 1. Photograph of patient in position for air myelography. The oxygen is injected through an open 3 way stopcock (1) which is connected to a manometer (2) which monitors intrathecal pressure. A water trap (3) is interposed in tubing from the stopcock to the manometer.

Laminagraphic cuts are obtained at 0.5 cm. intervals; one midline and two on either side of the midline. The first series of laminagrams is obtained in flexion. The pressure in the spinal subarachnoid space is checked after the initial series and usually additional oxygen is required to again raise the pressure to between 300 and 500 mm. of water. Following this, a second series of laminagrams is taken with the neck in extension. Coned views are sometimes necessary to demonstrate abnormalities in the lower cervical canal in patients with thick shoulders. Roentgenograms are also taken of the thoracic and lumbar regions.

At the conclusion of the procedure, the needle is removed and the patient is transported to his room in a head down position.

To reduce the probability of escape of oxygen intracranially with its attendant headache and discomfort, the patient is kept in a 20 to 30 degree Trendelenburg position for 6 hours following the procedure. He is then placed flat on his back for 12 hours and is allowed gradual elevation to the erect position over a 48 hour period.

ANATOMY

The cervical spinal canal is triangular in shape. The bony canal is formed by the

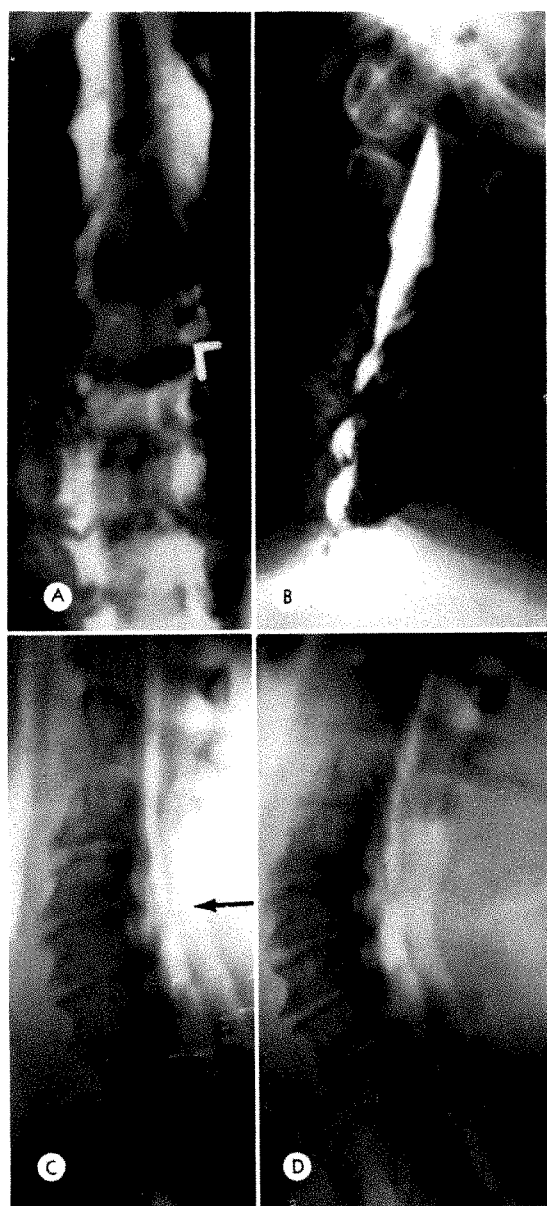


FIG. 2. (A-D) A 60 year old female with long tract and lower motor neuron signs which persisted following laminectomy. Preoperative oil myelograms failed to indicate cord atrophy. Persistence of symptoms led to postoperative air myelography which revealed considerable cord atrophy (←).

posterior surface of the vertebral bodies anteriorly, the pedicles laterally, and the lamina posteriorly. In addition to the spinal cord, the soft tissue contents of the spinal canal include the posterior longitudinal

ligament anteriorly and the ligamentum flavum posterolaterally.

The sagittal diameter of the spinal canal from the C₃-C₄ interspace to the C₆-C₇ interspace measures between 12 to 22 mm. in the normal person with an average of 17 mm.¹²

The cervical spinal cord, as seen on the oil myelogram in frontal projection, occupies approximately two-thirds of the width of the subarachnoid space below C₄. In the translateral view, the cervical spinal cord is approximately 3 mm. from the ventral surface of the oil column.¹¹

The sagittal diameter of the cervical spinal cord, as seen on the air myelogram, measures approximately 9.5 mm. at C₃-C₄ and tapers to 8 mm. at C₆-C₇ with a variation of plus or minus 1 mm. The subarachnoid space ventral to the cord, as seen on the air myelogram, measures 4 to 7 mm. with an average of 5 mm. In the normal person, the spinal cord remains separated from the anterior wall of the spinal canal by this air-filled subarachnoid space both in flexion and extension.²

MATERIAL

In this series of 29 patients, pantopaque myelography preceded air myelography and the examinations were usually done at the same sitting. The series was not entirely random, as frequently the results of the pantopaque or gas myelography were so conclusive that additional studies were deemed unnecessary. Also, the combined study requires approximately 3 hours so that the general physical status of some of the patients had to be taken into consideration.

DISCUSSION

Some form of contrast examination is necessary to evaluate the spinal canal and its contents in patients with cervical spondylosis. Even in patients where posterior osteophytic bars are demonstrable on plain roentgenograms, if the sagittal diameter of the spinal canal is adequate, there may be

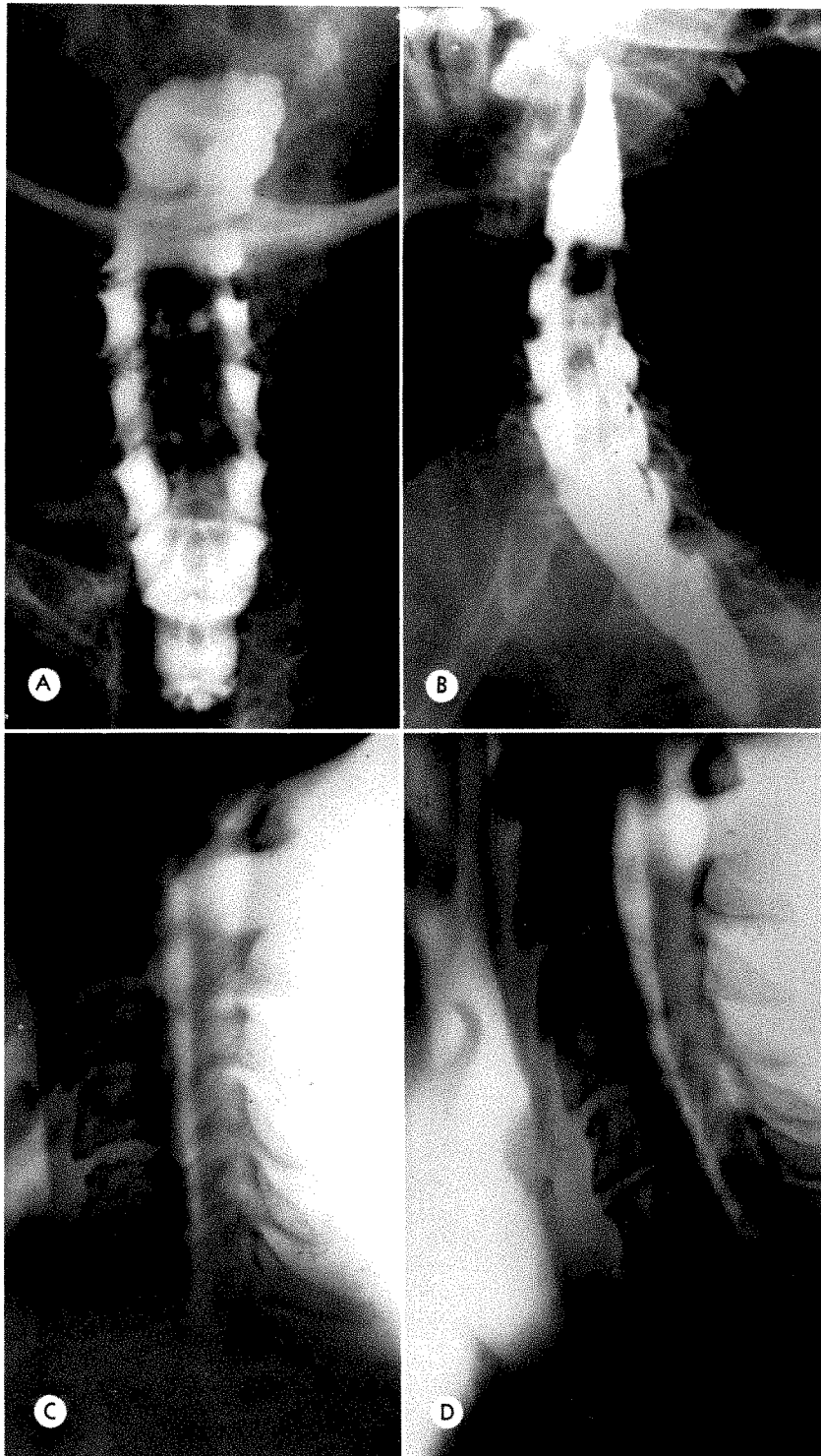


FIG. 3. (A-D) A 61 year old male with atrophy of intrinsic muscles of right hand. Oblique projections with oil myelography can successfully demonstrate encroachment on nerve roots (→) which is not demonstrable on air myelograms.

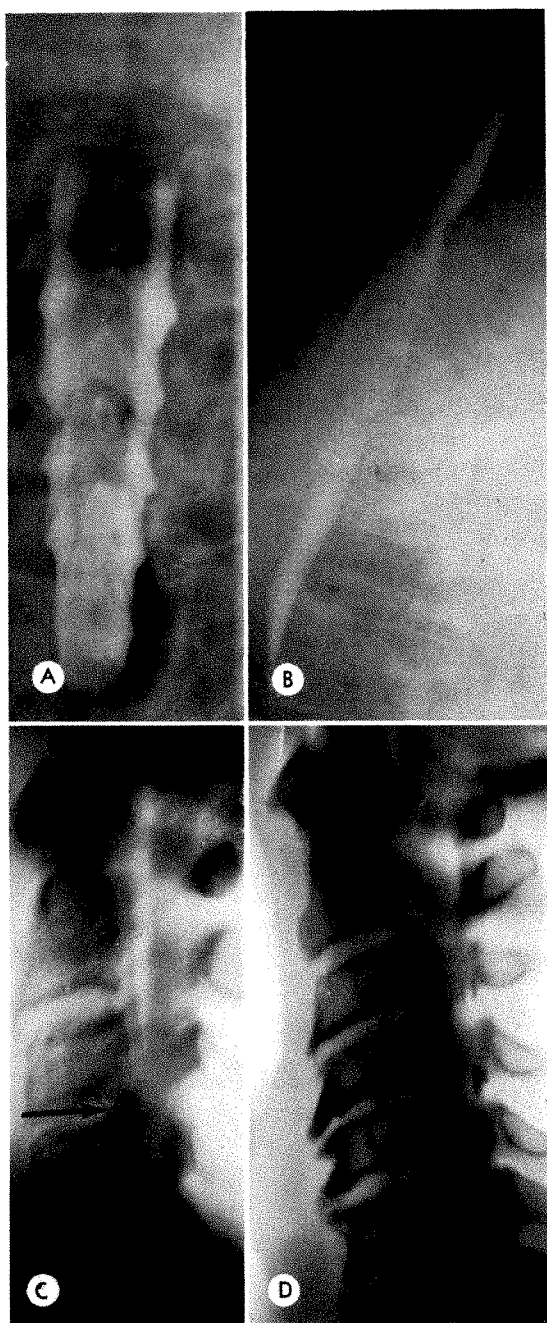


FIG. 4. (A-D) A 61 year old male with stiffness in his legs and numbness in all extremities. A complete block to the cephalad floor of oil may occur with cervical spondylosis. Air myelography (→) via the suboccipital route can clarify the differential diagnosis of tumor.

no encroachment upon the spinal cord. On the other hand, spinal cord atrophy may already be present from encroachment by

the osteophytic bars and surgery cannot be expected to benefit these patients. One of our patients who had oil myelography prior to surgery had persistence of signs and symptoms following laminectomy. Post-operative gas myelography demonstrated spinal cord atrophy (Fig. 2, A-D).

Most commonly in this country, pantopaque myelography is used to study cervical spondylosis. When the pathology is confined to lateral osteophytes encroaching upon the intervertebral foramina, the pantopaque myelogram is more informative (Fig. 3, A-D). However, in only 2 patients in this series was the pathology confined to lateral osteophytes. With cervical spondylosis, the patient is unable to fully extend the head and neck and may have considerable cervical pain which limits the application of pantopaque myelography. The normal cervical lordotic curve may be straightened or reversed so that the cervical canal cannot be filled adequately with pantopaque. In this series, 3 patients had moderate to marked intracranial spill of the pantopaque. The physical properties of pantopaque are such that midline defects or very small lateral protrusions may be masked by the density of the pantopaque. When there is a complete block, it is sometimes advantageous to demonstrate the lower level of the block by pantopaque myelography and the upper extent of the block by suboccipital air myelography (Fig. 4, A-D).

TABLE I

	Patients	
	Air	Pantopaque
Possible to measure anteroposterior diameter of the cord	26	4
Evidence of ligamentum flavum encroachment	0	5
Demonstration of cord atrophy	6	0
Mid-line protrusion	9	9

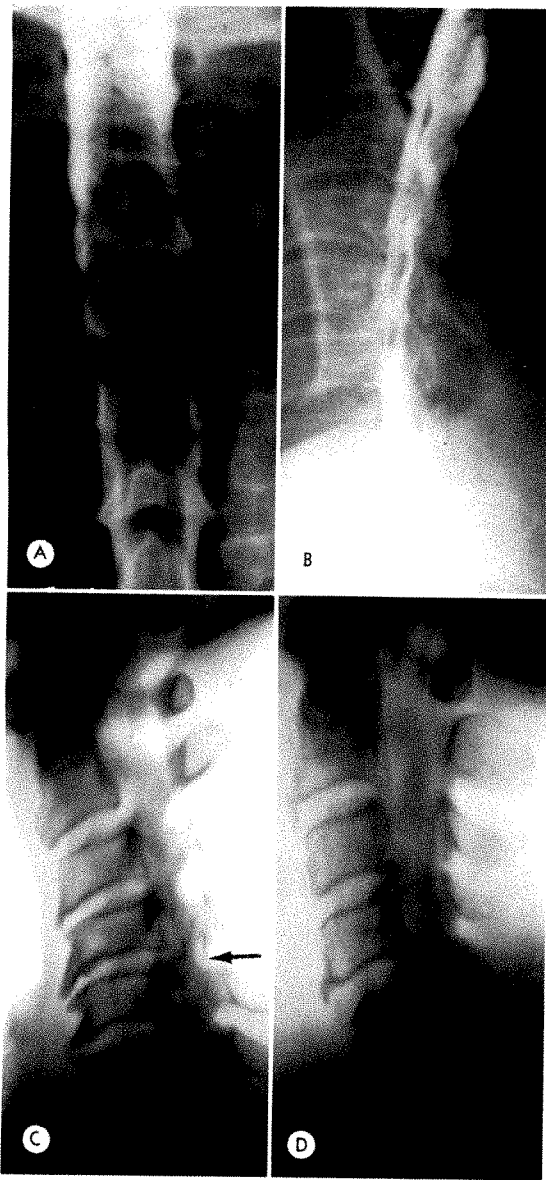


FIG. 5. (A and B) A 52 year old male with spasticity and hyperflexion. Oil myelograms showed compression of cord simulating intramedullary tumor. (C and D) Air myelograms demonstrated the actual presence of atrophy (←).

Air myelography distends the spinal subarachnoid space with oxygen and permits complete evaluation of the spinal canal. An accurate measurement of the sagittal diameter of the spinal cord can be made (Table 1). The spatial relationships of the spinal cord and the anterior and posterior boundaries of the spinal canal are

readily seen. The patient plays a passive role in air myelography, and during the examination, disturbances in cervical spine mobility are not nearly as important as they are in pantopaque myelography. Protrusions and their influence on the cord in flexion and extension can be evaluated. Four patients showed accentuation by motion. In this series, there were 3 patients in whom the cord appeared widened on the oil myelogram because of the compression. The appearance simulates syringomyelia or intramedullary tumor (Fig. 5, A-D). Atrophy of the cord is readily demonstrable with air myelography, whereas we have been unable to make this diagnosis with pantopaque myelography (Table 1).

SUMMARY

Pantopaque myelography will in most cases give more information with greater facility than will air myelography. However, the diagnosis of atrophy of the spinal cord can seldom be made by pantopaque myelography. Patients with atrophy of the spinal cord secondary to cervical spondylosis do not demonstrate significant improvement following surgery; therefore, air myelography is a very important adjunct to the preoperative evaluation of patients with cervical spondylosis.

William Weidner, M.D.
Department of Radiology
University of California
Los Angeles Center for the Health Sciences
Los Angeles, California

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PAGET'S DISEASE IN THE CERVICAL SPINE*

By GEORGE P. JANETOS, M.D.

PALO ALTO, CALIFORNIA

PAGET'S disease in the cervical spine is relatively rare. In 10 published articles, only 26 cases are reported (Table 1). Schmorl found 10 instances of cervical spine involvement in autopsy material. The purpose of the author is to present 2 such cases, tabulate the previous cases and call attention to possible complications.

The disease is most frequently seen in the pelvis, femur, spine, skull and tibia. Dickson *et al.*³ reported on 367 cases of Paget's disease and found the disease in the lumbar spine 103 times, the thoracic spine 51 times,

and the cervical spine 6 times. Likewise, Gutman and Kasabach⁴ cited 51 cases in lumbar spine, 26 in the thoracic spine, and 3 in the cervical spine. One hundred unselected cases of Paget's disease from our clinic were reviewed. Cervical spine roentgenograms were available in 23 of these. The cervical spine was involved 2 times, the thoracic 6 times, and the lumbar spine 25 times.

Fracture is the most common complication of Paget's disease,¹⁰ occurring 8 times in these 100 patients. The characteristic enlargement of the bone occurs in the spine.

TABLE I
PAGET'S DISEASE IN THE CERVICAL SPINE

Author(s)	No. of Cases	Year	Age	Sex	Segments Involved	Cervical Spinal Cord Compression
Gutman and Kasabach ⁴	5	1936	?	?	?	0
Garcin <i>et al.</i> ⁵	1	1937	61	M	C3-4	+
Schwarz and Reback ⁹	2	1939	57	M	C4-6	+
			60	M	C7 to sacrum	0
Turner ¹²	2	1940	60	M	C4-D5	+
			66	M	C7-8	+
Hillman ⁶	1	1941	44	F	C6	+
Dickson <i>et al.</i> ³	6	1945	?	?	?	0
Whalley ¹³	1	1946	66	M	C1-2	+
Teng <i>et al.</i> ¹¹	1	1951	65	M	Entire spine	0
Rosenkrantz <i>et al.</i> ⁸	6	1952	?	?	?	0
Ramamurthi and Visvanathan ⁷	1	1957	60	M	C1-2	+
Janetos (present report)	2	1965	55	M	C5	0
			78	M	C2-6	0
Totals	28					7

* From the Department of Radiology, Palo Alto Medical Clinic.

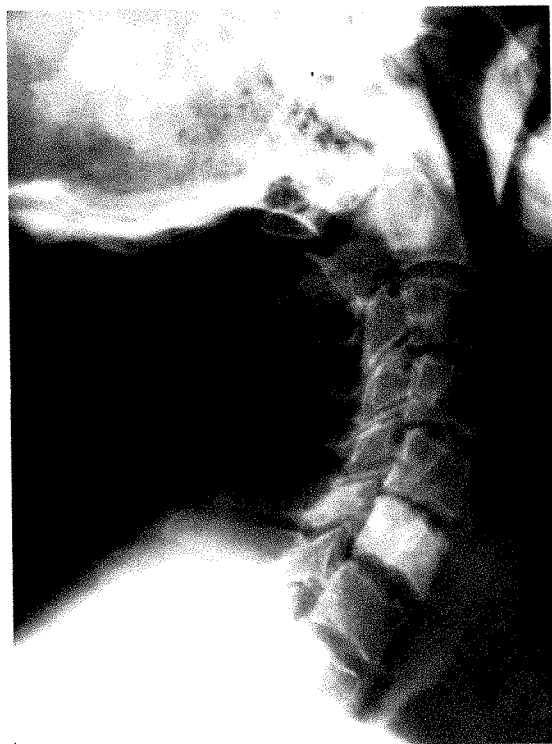


FIG. 1. Characteristic enlargement and sclerosis of the Paget's vertebra.

The spinal cord can be compressed by one or both of these modalities. This is not commonly reported but, nevertheless, remains a feared complication. Garcin *et al.*³ described the first verified case of spinal cord compression associated with Paget's vertebra at C3-C4.

REPORT OF CASES

CASE I. A white male office worker, aged 55 years, was struck from behind while driving his car. He developed neck pain and this prompted cervical spine roentgenograms. The 6th cervical vertebra was found to be enlarged and sclerotic (Fig. 1). The 5th disk space was narrowed. The remainder of the cervical spine was demineralized. Roentgenograms of the entire spine and pelvis demonstrated Paget's disease in the sacrum and pelvis. The sacroiliac joints were obliterated.

No complications occurred. The patient was an enthusiastic horseman and was advised to forego this sport because of a potentially fragile cervical vertebra.

CASE II. A 78 year old retired white male was

known to have widespread Paget's disease. He had suffered fractures of the humerus and clavicle. Cervical spine roentgenograms showed the Paget's vertebra at C2-C6 (Fig. 2).

DISCUSSION

The etiology of the disease is unknown. There is no proof of a bacterial agent. It has been called "osteitis deformans" because of the belief that it was an infection. The disease is limited to bone. Roentgenographically, there is demineralization first. This is best seen in the lower extremity when a V-shaped margin is present at the distal edge of the Paget's bone. Brailsford¹ attributes this to the stripping of the periosteum as would result if you were to strip paper from a cylinder. In the wake of the osteoporosis, the bone is rebuilt with an increased size and disorganized pattern. Large vascular spaces are seen in histopathologic studies. Moore⁶ suggested that a



FIG. 2. Pagetoid changes in varying degrees of the second through sixth vertebrae.

disease of the autonomic nervous system might account for the increased vascularity with resultant osteoporosis. The concept is plausible. It might be combined with an osteotrophic agent which is locally advancing and affects the autonomic nervous system of bone—the glomic apparatus.

Paget's disease in the spine can cause chronic spinal cord and nerve root compression. Fracture changes the clinical picture to an acute one. It follows then that Paget's disease is an important, although infrequent, neurologic problem. When the characteristic changes are found in some portion of the skeleton, the patient should have a simple roentgenographic survey of the spine. Should the vertebrae be involved, appropriate activity restrictions may circumvent paraplegia.

SUMMARY

Two cases of Paget's disease involving the cervical spine are reported, bringing the total of cases in the literature to 28. Cord compression was present in 7. Patients afflicted with the disease should have a roentgenographic survey of the spine and appropriate care designed to prevent quadriplegia.

Department of Radiology
Palo Alto Medical Clinic
300 Homer Avenue
Palo Alto, California 94301

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COR PULMONALE IN KYPHOSCOLIOSIS*

ANGIOCARDIOGRAPHIC FEATURES OF A CASE

By ISRAEL STEINBERG, M.D.†

NEW YORK, NEW YORK

IN THEIR classic monograph, Bergofsky, Turino, and Fishman,¹ in 1959, reported a case of kyphoscoliosis with cardiorespiratory failure. The patient, a woman, was studied at the Presbyterian Hospital, New York, New York, in 1956, and found to be in Class II cardiorespiratory failure with dyspnea on exertion. Nine years later, in 1965, progressively severe dyspnea, asthmatic attacks, constant backaches, with fleeting numbness and tingling of the lower extremities prompted her admission to the Hospital for Special Surgery. Repeat respiratory physiologic studies showed slight decrease in pulmonary function as compared to 1956. A significant finding, however, was a mildly elevated venous pressure. Because of this, angiocardiology was done in order to visualize the degree of pulmonary arterial and venous distortion, the size of the pulmonary artery, and the size of the cardiac chambers. These data are the chief reason for this report, especially because the angiocardiology findings in cor pulmonale secondary to kyphoscoliotic cardiorespiratory disease have only rarely been recorded.^{4,5}

REPORT OF A CASE

K.S. was 19 years old and 142 cm. tall at the time of study at the Presbyterian Hospital in 1956.¹ Her spinal deformity was of idiopathic etiology and had begun at the age of 10 years. The direction of convexity was to the left with the apex of the primary curve at the fourth thoracic spine. The degree of scoliosis was 130, the degree of kyphosis was 135, and the thoracic vertebrae in the primary curve extended from the sixth cervical to the second lumbar spines. She complained of dyspnea on moderate exertion and tachycardia. Pulmonary function studies in 1956 had shown that the respiratory

capacity was 38 per cent of the predicted normal value; the vital capacity, 37 per cent; the residual volume, 32 per cent; and the total capacity, 35 per cent. There was also diminution of ventilation; but diffusion of the respiratory gases was normal.

Since discharge from the Presbyterian Hospital the patient has had recurrent and increasingly severe attacks of asthma which had begun

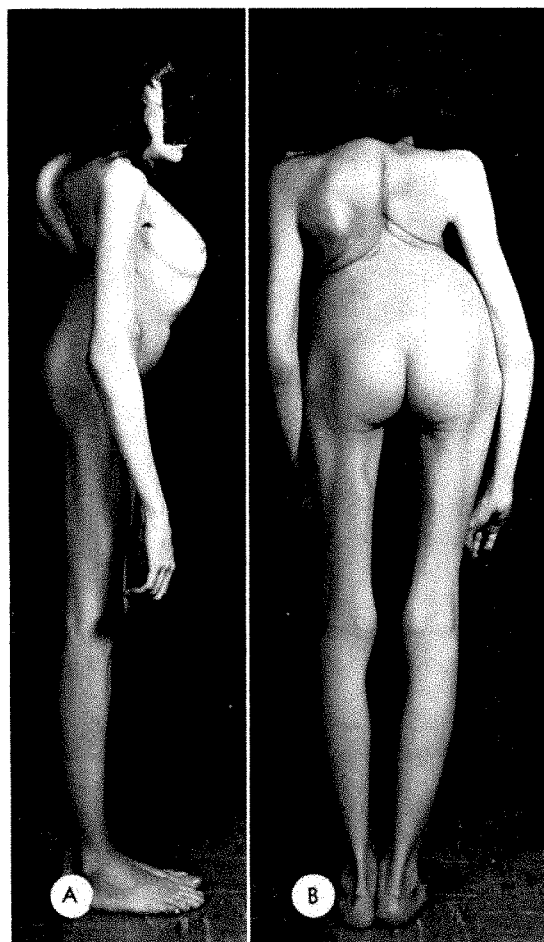


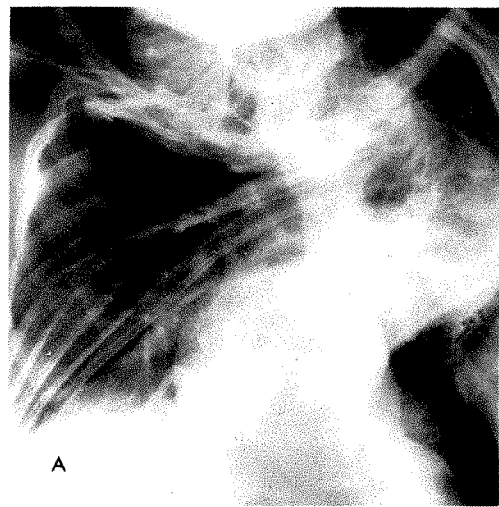
FIG. 1. (A) Side photograph of a 28 year old woman with severe kyphoscoliosis. (B) Dorsal view showing the left-sided thoracic deformity.

* From the Departments of Radiology and Medicine, The New York Hospital-Cornell Medical Center, New York, New York. This work was supported by the Health Research Council of the City of New York under contract U-1694.

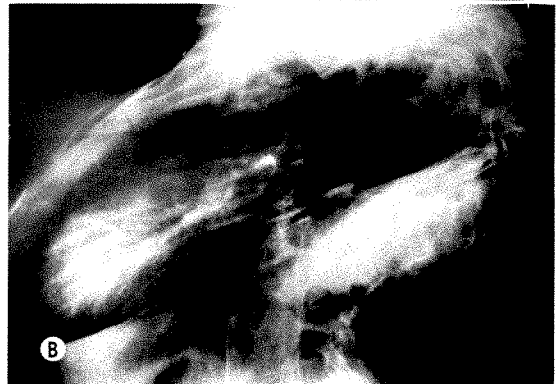
† Recipient of Career Scientist Award of the Health Research Council of the City of New York under contract I-255 and U-1694.

at the age of 13 years. Dyspnea on slight exertion developed and she was unable to walk more than 1 block. Constant and increasing backache persisted and on several occasions there was numbness and tingling of the feet and toes. On physical examination, on this admission in May, 1965, she appeared older than her age of 28 years, measured 54 inches in height (137 cm.), and weighed 54.5 kg. The thorax was kyphoscoliotic (Fig. 1, *A* and *B*). The respirations were 26 at rest and 60 per minute after exercise. The lungs were clear. There was a holosystolic (Grade 2 to 4) murmur heard loudest below the left clavicle. The blood pressure was 100/80 mm. Hg. Pulmonary function tests had not changed much from the values recorded at the Presbyterian Hospital in 1956.¹ The pH blood determinations on the admission in 1965 were 7.43 at rest and 7.39 after exercise. The arterial oxygen saturation was 96.4 per cent at rest and 96.3 per cent after exercise. Only the venous pressure was mildly elevated, measuring 180 mm. H₂O 10 cm. from the table top and 70 mm. at the angle of Louis. The electrocardiogram was normal. Cardiac catheterization was not done during this admission; in 1956 at the Presbyterian Hospital, the pulmonary blood pressure was 24/15 at rest, and 36/20 mm. Hg after exercise, and the pulmonary wedge pressure was normal.

The conventional roentgenograms of the chest on this admission showed marked kyphoscoliosis of the spine, severe deformity of the thorax, and convex bowing of the sternum. The left hemithorax was markedly compressed and the heart was displaced forward and retrosternally (Fig. 2, *A* and *B*). Biplane, simultaneous, intravenous angiocardiology showed the superior vena cava in the usual position just to the right of the spine. The right atrium and ventricle were, however, rotated into the right hemithorax in the position of about a 15–20 per cent left anterior oblique view. The right ventricular wall was slightly enlarged and measured 5 mm. (average normal measurement is 2–3 mm.). The pulmonary artery and branches were enlarged. The left pulmonary artery was foreshortened and crowded into a small left hemithorax while the right pulmonary artery branches were distended and spread widely apart in the larger right hemithorax (Fig. 3, *A* and *B*). At the time of opacification of the left heart structures, the right pulmonary veins were visualized but the left pulmonary veins



A



B

FIG. 2. (*A*) Frontal teleroentgenogram of the chest showing severe left-sided kyphoscoliosis. The trachea is deviated towards the right, the right lung is larger than the left, and the heart and great vessels are indiscernible. (*B*) Lateral roentgenogram of the chest shows the heart to be retrosternal, the thorax deformed, and narrowed.

were partially hidden by the misplaced left ventricle and aorta. The left ventricle and aorta were also rotated into the left anterior oblique position, although the roentgenogram was made in the frontal view (Fig. 4*A*). The ascending aorta was placed retrosternally, but the descending portion followed the curve of the spine⁵ (Fig. 4, *A* and *B*).

DISCUSSION

Since the time of Hippocrates, dyspnea, cyanosis, and sudden death have been recognized as the fate of hunchbacks.^{1–3,6–9} Physiologic studies of kyphoscoliotic patients began in 1854 when Schneevogt¹¹ measured the diminished vital capacity with

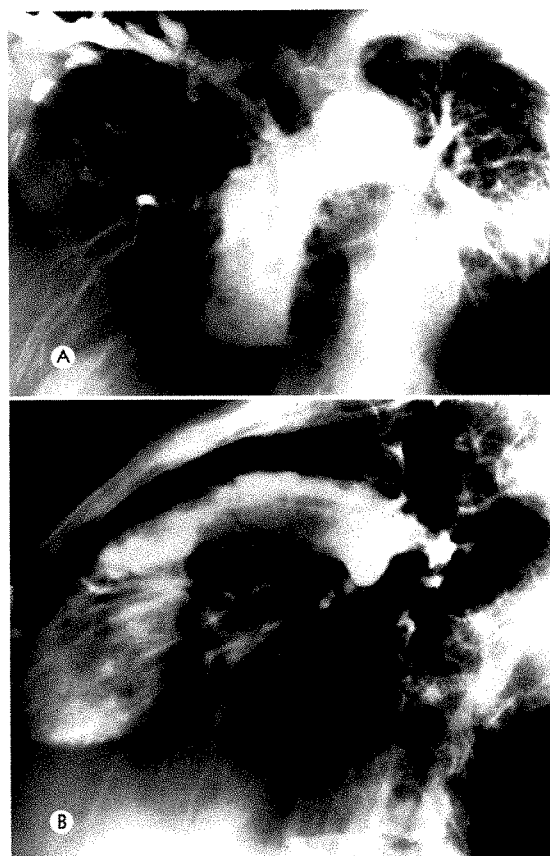


FIG. 3. (A) Frontal angiocardigram shows the superior vena cava in its usual midline position. The heart is rotated into the left anterior oblique position. The right ventricular wall and the main pulmonary artery are enlarged. The branches of the right pulmonary artery are widely spread apart. The left pulmonary arterial tree appears to be larger than the right and its branches are crowded into the small left hemithorax. (B) Biplane lateral view of A.

a spirometer. In 1939, Chapman, Dill, and Graybiel⁸ used modern physiologic respiratory techniques for study of a series of cases of kyphoscoliosis. In 1956, Iticovici and Lyons¹⁰ performed ventilatory and lung volume determinations of patients with chest deformities. In 1958, Hanley *et al.*⁹ especially investigated the heart failure features in the disorder. Finally, in 1959, Bergofsky and co-workers¹ made the definitive study of the disease.

In kyphoscoliosis, there is an excessive anteroposterior curvature, a lateral curva-

ture, and an associated rotation of the spine and trunk (Fig. 1, A and B; and 2, A and B).¹² Poliomyelitis and idiopathic etiologies account for 75 per cent of the cases in childhood, and during this period there is a greater frequency of the disease among girls; a 4:1 ratio of females to males exists. In adults, probably because those affected with severe chest deformities rarely survive, the ratio becomes almost equal.²

Bergofsky, Turino, and Fishman¹ have shown that generalized alveolar hypoventilation is a prime defect in kyphoscoliosis. This leads to arterial hypoxemia and hypercapnea. In contrast to chronic pulmonary emphysema, the alveolar hypoventilation in kyphoscoliosis is due to anatomic re-

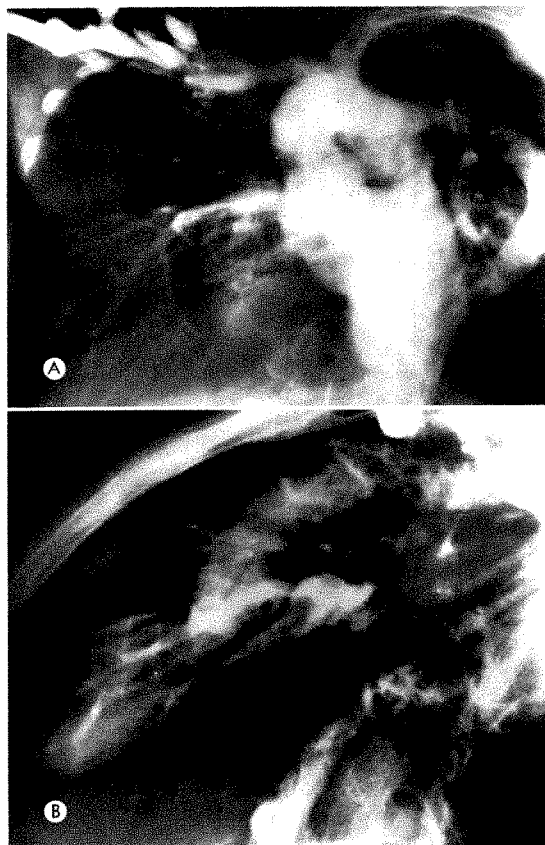


FIG. 4. (A) Frontal angiocardigram showing normal pulmonary veins, left atrium, and aorta. The descending aorta is markedly displaced, accommodating to the deformed spine. (B) Lateral biplane view of A. Note that the aorta, although intact, fits into the gibbus of the spine.

striction of the chest rather than to bronchial obstruction and uneven distribution of inspired air. Pulmonary hypertension (cor pulmonale) is present in some cases at rest and is elicited in others during exercise. The elevated pulmonary pressure is apparently secondary to an abnormal resistance to blood flow through the pulmonary vascular bed. The factors responsible for the increased pulmonary resistance are believed to be mechanical compression of the vascular bed, anatomic thickening of the precapillary vessel wall, and effects of hypoxemia.

For comparison with the case described above, the conventional and contrast roentgenograms of a 34 year old man, also with cardiopulmonary failure (cor pulmonale) due to severe kyphoscoliosis of the right hemithorax, are shown in Figure 5, *A* and *B*; 6, *A* and *B*; and 7, *A* and *B*. In this patient, the anterior margins of the rib cage are tilted so far forward that the rib cage extends into the pelvis (Fig. 5*A*). The lower halves of both hemithoraces are so obscured by the kyphoscoliosis and elevated diaphragms that it is impossible to estimate the size of the heart. Only the upper portions of the thorax are lucent and contain lung. In the left hemithorax the air in the stomach, although below the diaphragm, hugs the left cardiac border and stimulates a diaphragmatic or esophageal hernia. In the lateral view, the heart reaches the undersurface of the sternum and apparently causes the sternum to bulge convexly forward. The spinal gibbus occupies almost one-half of the anteroposterior diameter of the thorax (Fig. 5*B*).

The frontal angiocardigram shows the superior vena cava to be in the normal position. The right heart chambers are obscured by the spinal deformity, but the main pulmonary artery is visualized and enlarged. The right pulmonary artery hugs the hilus; its branches appear large at their origins and at the midzones of the right lung but fade at the periphery of the lung. A similar situation is present in the left hemithorax, but the left lung appears smaller than the

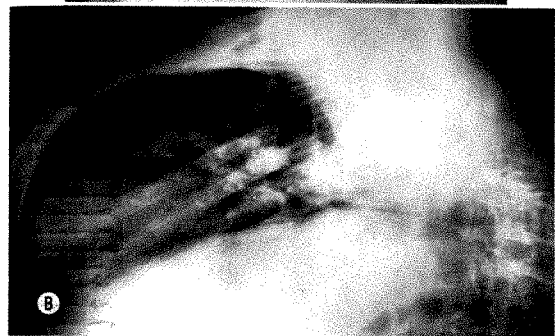
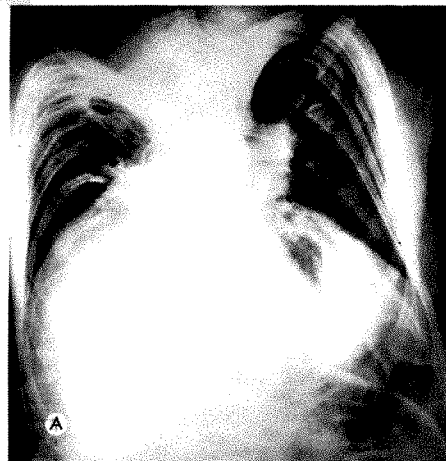


FIG. 5. (*A*) Frontal teleroentgenogram of a 34 year old man with severe right-sided kyphoscoliosis and cardiorespiratory failure (dyspnea on exertion). Note that the anterior rib cage extends into the pelvis. The cardiac shadow is obscured by the spinal deformity and by elevated diaphragms. (*B*) Lateral roentgenogram of the chest showing the tremendous gibbus which displaces the heart anteriorly and the sternum forward.

right (Fig. 6*A*). The left heart chambers are also obscured by the spinal deformity, but the aorta and brachiocephalic artery are well visualized. The aorta is somewhat unfolded, but the brachiocephalic branches are normal. The heart, right and left sides are not unusually large (Fig. 6*B*). The lateral angiocardigram is revealing, the right ventricle and pulmonary artery are enlarged while the pulmonary arterial tree is markedly distorted (Fig. 7*A*). The left atrium, pulmonary veins, and aorta are normal. Of interest is the markedly kinked descending aorta which while intact fits into the spinal deformity (Fig. 7*B*). The lateral views also show the tremendous

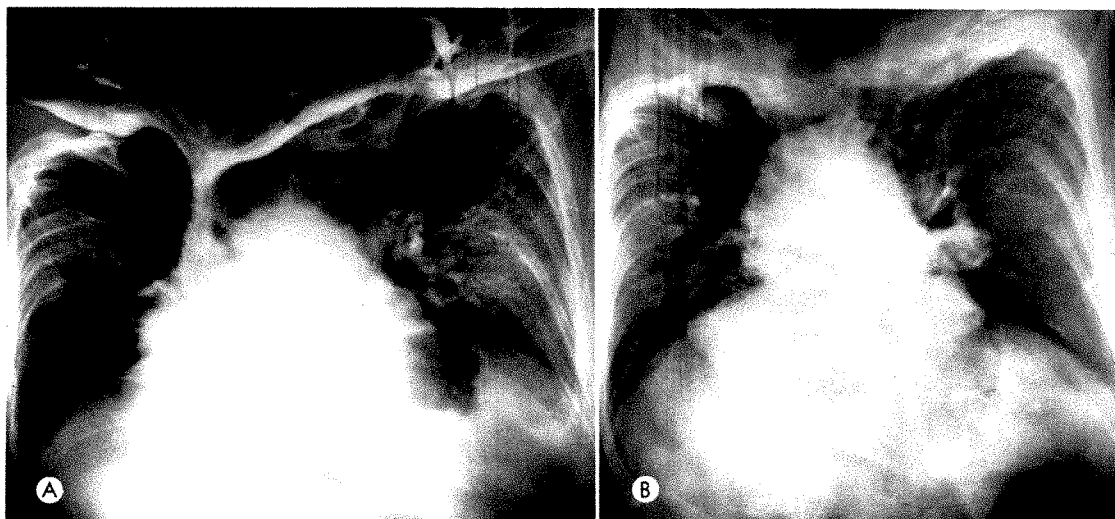


FIG. 6. (A) Frontal angiocardiogram showing the normal position of the superior vena cava. The right cardiac chambers are obscured by the spinal deformity, but the pulmonary artery is enlarged. The right pulmonary arterial circulation is attenuated; the outer pulmonary zone is especially small. The left pulmonary arterial circulation, while larger, is also attenuated at the periphery. (B) Left heart angiocardiogram showing that the left heart and aorta are not enlarged.

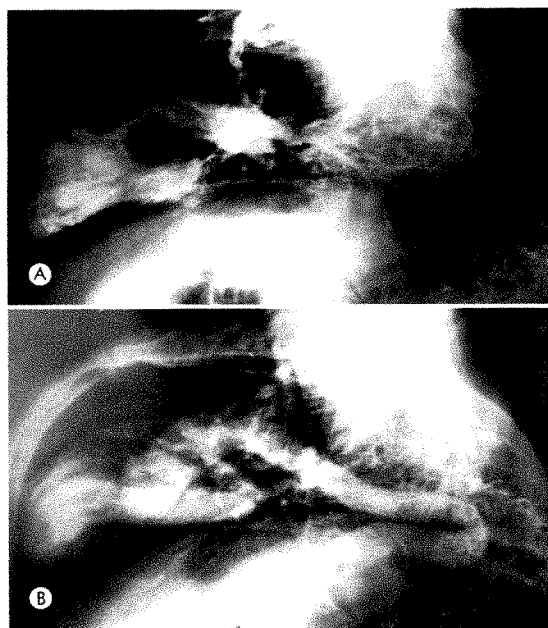


FIG. 7. (A) Lateral angiocardiogram showing enlargement of the right ventricle and pulmonary artery. Note the marked anterior location of the heart and small size of the thoracic cavity. (B) Later in the series, the left atrium, ventricle, and aorta are normal but the descending aorta follows the contour of the spine. (Reproduced by permission from *Radiology*.⁵)

narrowing of the thorax resulting from severe kyphoscoliosis.

In earlier publications from this center the angiocardiographic findings in kyphoscoliosis have been described.^{4,5} The cardiovascular structures apparently accommodate to the severe deformity of kyphoscoliosis by rotating into the available space in the thorax. When the left thorax is the site of kyphoscoliosis, the cardiovascular structures assume the left anterior oblique position in the right hemithorax (Fig. 2, A and B; 3, A and B; and 4, A and B). When the kyphoscoliosis involves the right hemithorax, rotation of the heart towards the left side causes it to assume a right oblique position. Such was the situation in 2 patients with right-sided kyphoscoliosis studied angiocardiographically and previously reported.^{4,5} In the severe right-sided kyphoscoliosis patient described above, the cardiovascular system remained in a central position in front of the spine, but was dislocated far anteriorly, producing marked anterior bowing of the sternum (Fig. 5B, 6B, and 7B).

Pulmonary artery enlargement in ky-

phoscoliosis is apparently related to the pulmonary hypertension and cor pulmonale that follows cardiorespiratory failure. In the case reported above, pulmonary hypertension was documented at cardiac catheterization 9 years prior to the angiocardiology. Although considerable deformity of the pulmonary circulation results from the distorted chest caused by kyphoscoliosis, the evidence points to the changes in the pulmonary vascular bed being responsible for the increased pulmonary resistance, hypertension, and chronic cardiopulmonary failure, and not *per se* the misshapen lungs.¹

SUMMARY AND CONCLUSION

Angiocardiological studies of a 28 year old woman who has had cardiopulmonary failure for many years following a severe left-sided kyphoscoliosis revealed cor pulmonale. Pulmonary function and cardiac catheterization studies, made 9 years earlier, had shown marked pulmonary function deficits and pulmonary hypertension. Cardiac catheterization was not repeated during this admission, but pulmonary function studies showed slight further decrease in pulmonary function. Increasing dyspnea, backache, and symptoms of spinal cord compression made spinal fusion imperative. Although enlargement of the right ventricle and pulmonary artery and marked deformity of the vascular tree were demonstrated, these data did not preclude treatment of the threatening spinal cord catastrophe. Because the heart and cardiovascular system may be obscured by the kyphoscoliosis, angiocardiology is recommended for substantiating the diagnosis of cor pulmonale and for proper delineation

of the distorted cardiovascular structures.

The New York-Cornell Medical Center
525 East 68th Street
New York, New York

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PROGRESSIVE VERTEBRAL INTERSPACE CHANGES FOLLOWING LUMBAR DISK SURGERY

By ROBERT M. LOWMAN, M.D., and FRANKLIN ROBINSON, M.D.
NEW HAVEN, CONNECTICUT

PROGRESSIVE degenerative changes of the intervertebral disk space and adjacent vertebral bodies, associated with protracted and disabling symptoms, may be encountered as infrequent sequelae of lumbar disk surgery. These observations are based upon a group of such patients, each of whom presented a typical syndrome of herniated lumbar disk, confirmed at operation and treated by excision of the herniated disk material. Suppuration did not occur in any of the surgical wounds nor were any cases complicated by bacterial infection of the vertebral body, extradural space or deep structures. In most of the patients, the symptomatology remained unexplained until the disclosure of the characteristic roentgenographic changes, several weeks or more following operation. Roentgenographic evidence of varying degrees of destruction of the adjacent vertebral bodies was observed, with progressive obliteration of the intervertebral disk space followed by reparative osseous changes. In one instance, solid fusion ultimately occurred across the intervertebral space. In the remaining cases, extensive osteophyte formation involving the anterior margins of the affected vertebrae was seen. Clinical improvement was accompanied by roentgenographically demonstrated fusion of the involved vertebral interspace.

The present study is based upon an evaluation of a limited number of cases, and several representative cases are discussed. The actual frequency of this unfortunate postoperative complication is perhaps speculative. The apparent low incidence may be explained by the self-limited nature of the process, for the lesion may occur and heal without recognition, the diagnosis remaining unestablished. Postoperatively,

the persistence of nonspecific lumbar complaints may not immediately be recognized as a reflection of a second vertebral pathologic process, since the symptoms may be rather bizarre and unassociated with fever.

The following cases are briefly presented.

ILLUSTRATIVE CASES

CASE 1. A.T., a 55 year old white male, abruptly developed, while shoveling snow, severe back pain radiating to the back of both knees. Neurologic examination suggested an intervertebral disk herniation at the L4-5 interspace which was confirmed by myelography (Fig. 1A). Removal of the herniated intervertebral disk was performed uneventfully on April 10, 1959. For 8 months thereafter the patient continued to complain of back pain. He was rehospitalized on December 14, 1959 with complaints of intense pain radiating down the anterior and lateral aspects of both legs to the knees. Roentgenographic examination demonstrated narrowing of the L4-L5 intervertebral space with loss of outline of the anterior inferior margins of the articular plate of the 4th lumbar vertebral body and minimal fragmentation and irregularity of the bone surfaces of the adjacent vertebral segment (Fig. 1B). Early marginal sclerosis in this region and minimal posterior displacement of the 4th lumbar vertebra, relative to the 5th, were present. The patient failed to respond to a 3 week course of bed rest and traction. Surgical exploration of the lumbar extradural spinal canal and of the 4th lumbar interspace failed to disclose evidence of a purulent process or recurrent intervertebral disk herniation.

Left hemifusion of the spinous processes and laminae of L4 through S1 was carried out. Cultures from the operative site were negative. The patient improved gradually thereafter. Roentgenographic studies on August 31, 1960, sixteen months following the second operative procedure showed further decrease of the intervertebral space with sclerosis of the ad-

From the Departments of Radiology, Neurosurgery and Pathology of the Yale University School of Medicine and the Yale-New Haven Medical Center, New Haven, Connecticut.

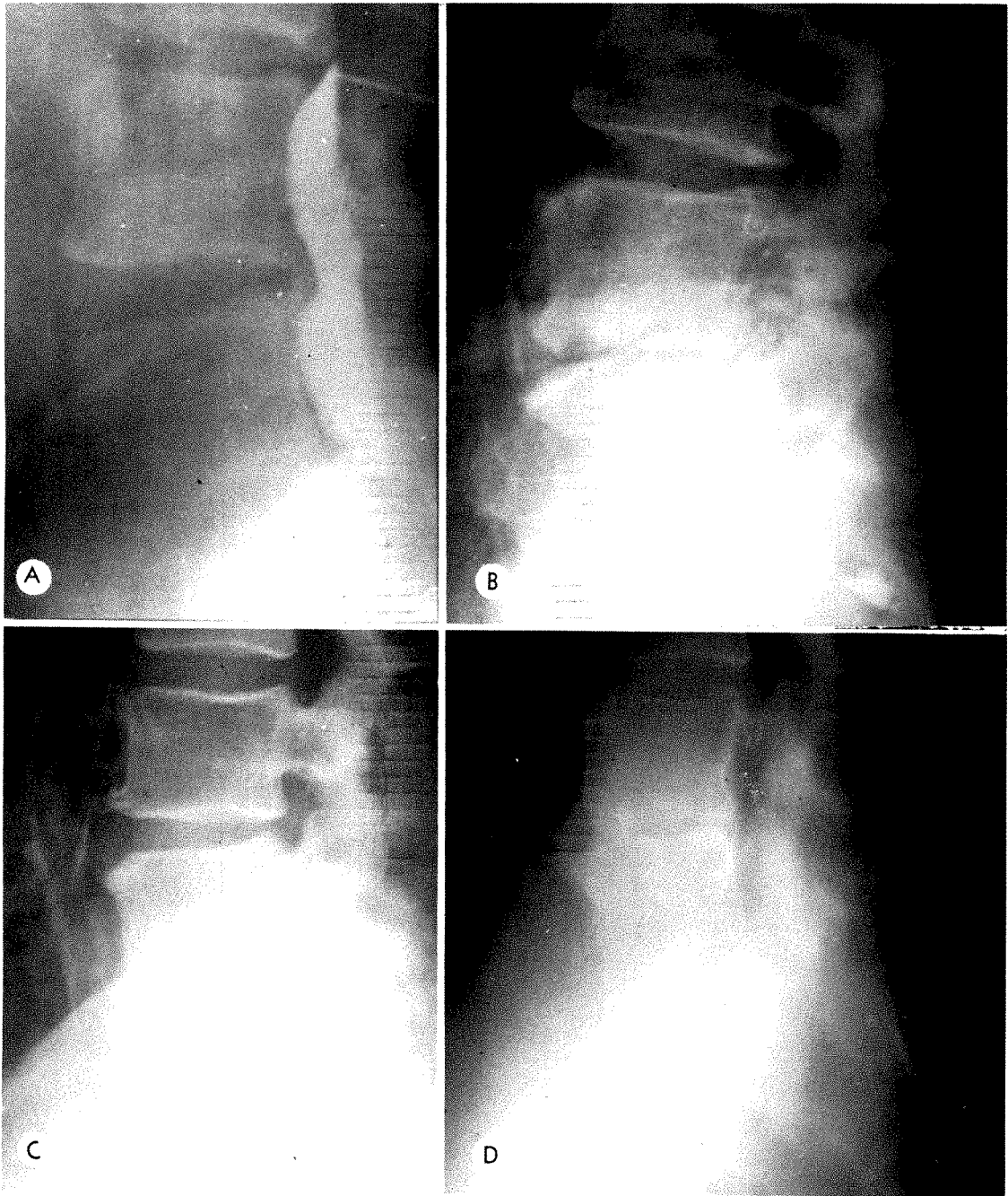


FIG. 1. Case 1, A.T. (A) Lateral myelogram made on April 3, 1959, prior to surgery. Note the sharp definition of the vertebral margins of the L4-L5 interspace. (B) Lateral study on December 21, 1959, shows (1) loss of the normal articular space, (2) loss of definition of bone margins adjoining the interspace, and (3) sub-articular sclerosis and osteophyte formation of L4-L5 vertebrae. These changes are most marked on the anterior inferior margins of the L4 vertebra. Minimal posterior luxation of L4 is shown. (C) Lateral study on August 31, 1960, shows reparative sclerotic changes of the vertebra with persistent narrowing of the L4-L5 interspace. (D) Lateral laminagram better defines the L4 interspace and the sentinel osteophyte formation along the anterior border of the interspace. Transosseous fusion has occurred.

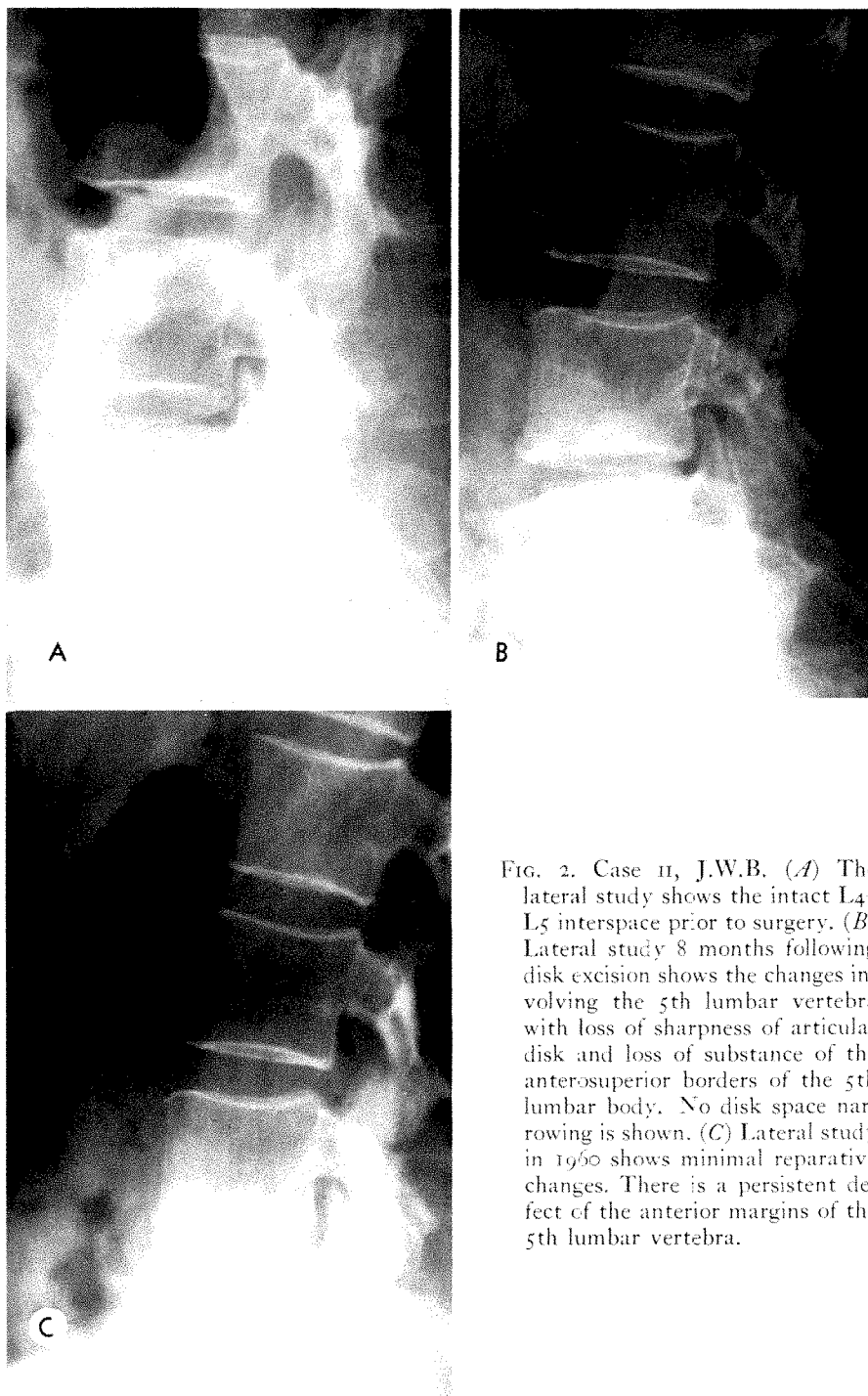


FIG. 2. Case II, J.W.B. (A) The lateral study shows the intact L4-L5 interspace prior to surgery. (B) Lateral study 8 months following disk excision shows the changes involving the 5th lumbar vertebra with loss of sharpness of articular disk and loss of substance of the anterosuperior borders of the 5th lumbar body. No disk space narrowing is shown. (C) Lateral study in 1960 shows minimal reparative changes. There is a persistent defect of the anterior margins of the 5th lumbar vertebra.

joining vertebral segments (Fig. 1C). A follow-up study 6 years later demonstrated complete transosseous vertebral fusion (Fig. 1D).

CASE II. J.W.B., a 48 year old white female, was admitted because of signs and symptoms consistent with herniated intervertebral disk at the L4-L5 interspace. A lateral view of lumbar spine (Fig. 2A) demonstrated an intact vertebral interspace. On May 26, 1959, surgery was performed and a freely-herniated disk fragment was removed from this level. Following operation, the patient complained of persistent back and leg pain. On February 1, 1960, roentgenograms of the lumbar spine demonstrated irregularities in the region of the superior articular plate of the 5th lumbar vertebra with some demineralization and loss of clarity of outline of the articular plateau (Fig. 2B). The cortical margins could not be defined. The patient was treated conservatively with bed rest and improved gradually. At no time was there fever, leukocytosis or increased sedimentation rate. Roentgenographic studies 1 year later demonstrated moderate irregularities associated with localized osteophyte formation and sclerosis of the superior articular plate of the 5th lumbar vertebra (Fig. 2C).

CASE III. J.C., a 29 year old white female, underwent operation for a herniated intervertebral disk at the L4-L5 interspace on October 9, 1958. Postoperatively, there was temporary relief from symptoms. Back pain recurred, however, 2 weeks following the operative procedure and discomfort became progressively worse. One month later, the 4th lumbar vertebral interspace was re-explored with a presumptive diagnosis of recurrent herniated disk. The operative procedure demonstrated no more than extradural scar formation. Lumbar pain persisted and the patient was readmitted on March 8, 1959, five months following her initial operative procedure. Laminagraphic studies demonstrated narrowing of the 4th lumbar vertebral interspace (Fig. 3B). The patient was placed in a short-leg spica for 1 month, but following removal of the cast, she again complained of low back pain of greater severity. Roentgen examination of the spine on April 24, 1959 demonstrated persistent narrowing of the L4 interspace. Laminagraphy confirmed the presence of the narrowing of the L4-L5 interspace and further demonstrated osteophyte formation along the anterior as-

pects of the 4th and 5th lumbar vertebrae, thought to represent reparative bone change. Marginal sclerosis at the intervertebral disk space was demonstrated. Subsequent roentgenographic studies on June 6, 1959 revealed further lipping and spurring of the adjacent vertebral bodies, and more pronounced narrowing of the interspace (Fig. 3C). The patient became progressively despondent and following an overdose of barbiturates was brought to the Emergency Room on August 16, 1960 dead. The spine was removed at autopsy. Sections and cultures revealed no evidence of localized infection. Postmortem roentgenographic studies of the lumbar spine showed persistent narrowing of the vertebral space but a significant reconstruction of the articular plates by new bone formation had occurred (Fig. 3D). The wedge defect along the posterior border of the 5th lumbar vertebra (Fig. 3E) is the site from which bone was removed for examination at necropsy.

DISCUSSION

The cases under study manifested consistently uniform bone deformities involving the margins of the disk space at the site of the operative procedure. The roentgenographic appearance seemed to represent a nonspecific reaction to injury, with necrosis of bone followed by proliferation of new tissue and calcification. There was evidence of progressive destruction of portions of the chondral plates of the vertebra with invasion of the spongiosa, followed by fibrosis and calcification. The similarity of these cases to those developing osteitis pubis following prostatectomy or abdominoperineal resection is evident; the onset of the symptomatology of the destructive phase together with the roentgenographic changes of early erosion followed by healing with sclerotic bone and subsequent fusion of the joint are common to both groups.⁸ The theories presented by Steinbach and associates¹² in connection with their studies on osteitis pubis should be considered at this point. These are: (1) trauma, (2) infection, and (3) impaired circulation. Steinbach *et al.* investigated the latter thesis by means of intraosseous venography in an attempt to understand the demineralization found

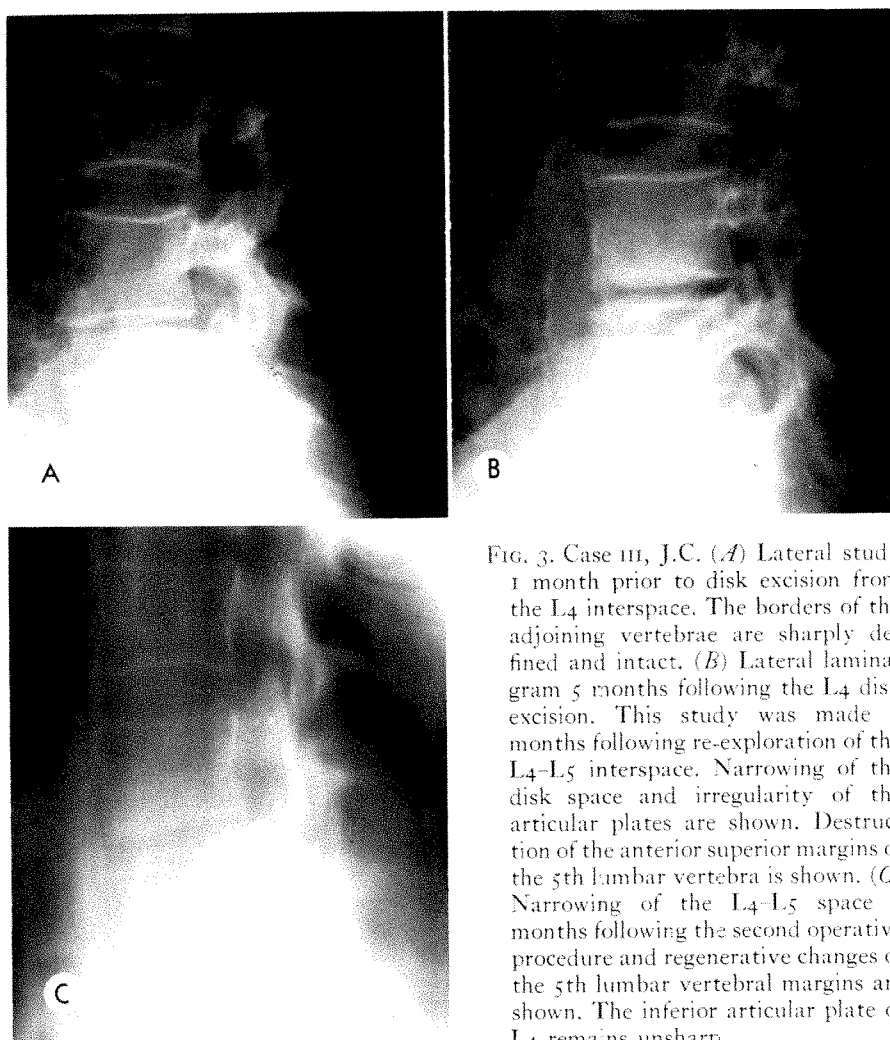


FIG. 3. Case III, J.C. (A) Lateral study 1 month prior to disk excision from the L4 interspace. The borders of the adjoining vertebrae are sharply defined and intact. (B) Lateral lamina-gram 5 months following the L4 disk excision. This study was made 4 months following re-exploration of the L4-L5 interspace. Narrowing of the disk space and irregularity of the articular plates are shown. Destruction of the anterior superior margins of the 5th lumbar vertebra is shown. (C) Narrowing of the L4-L5 space 9 months following the second operative procedure and regenerative changes of the 5th lumbar vertebral margins are shown. The inferior articular plate of L4 remains unsharp.

in association with osteitis pubis. Perhaps the findings of Steinbach *et al.* may explain, to some extent, the roentgenographic changes seen in the postoperative intervertebral disk cases. Steinbach and his co-workers observed distended venous channels which produced hyperemia and subsequent bone resorption with localized thrombophlebitis, and considered these to be the pathogenesis for the narrowing of the pubic symphysis, the subsequent marginal sclerosis and the final reparative changes in these structures. These postoperative roentgenographic findings have not been so studied by techniques of venography or arteriography. The effect of iatrogenic

trauma inherent in the surgical procedure is difficult to evaluate. That progressive degenerative disease can be activated and hastened by the mechanical manipulation associated with the operative procedure must, nevertheless, be considered.

The response of the intervertebral disk and the bone margins of the interspace may be the same whether the process is aseptic and degenerative or produced by bacterial infection. The earliest roentgenographic findings may be similar, though different in etiology. The development of an infection of the vertebral interspace seen after operation is most likely the result of direct implantation at the time of surgery.¹⁴ In a

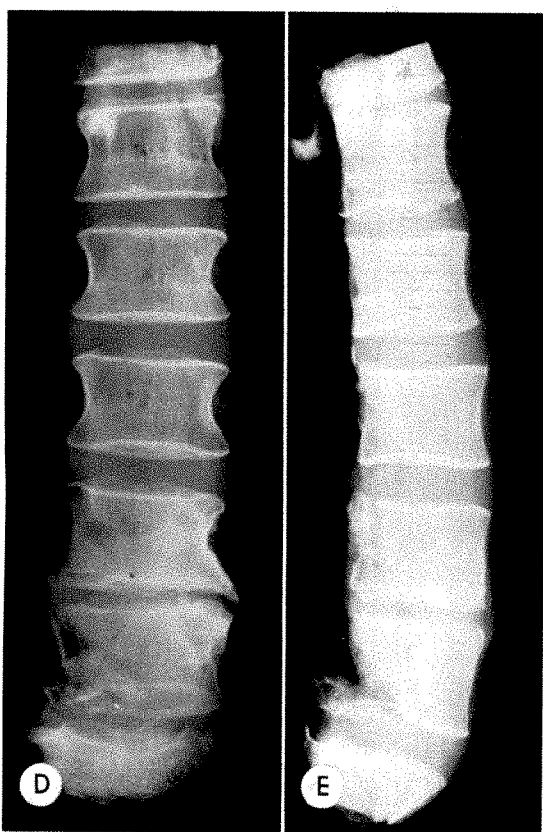


FIG. 3. (D) Anteroposterior and (E) lateral roentgen studies of the excised segments of the spine. Persistent narrowing of the interspace is shown. The postmortem examination of the bones showed reconstruction of the adjacent bone margins of the L4 interspace. Histologic studies revealed no evidence of osteomyelitis. The triangular defect of the 5th lumbar vertebra is the site where bone was excised for histologic studies.

survey completed at the Wadsworth General Hospital, 7 wound infections were noted following 343 operations for lumbar disk surgery.¹³ O'Connell¹¹ noted a 3 per cent incidence among 500 surgically treated patients, and Barr¹ described 5 cases of either infection of the wound or phlebotrombosis in 329 patients who had undergone disk excisions. Brussatis³ collected 4 cases of bacterial infection in the vertebral interspace following disk surgery in 200 patients from whom gross pus was recovered from the depth of the wound at the time of re-exploration; in 2 of his cases, *Staphylococcus aureus* was cultured, *Pseudomonas py-*

ocyanea in 1 case, and in the fourth case, no organism could be identified. In all of the 4 cases, serial roentgenographic studies demonstrated early erosion of the bony margins of the intervertebral disk followed by subsequent sclerosis of the adjacent vertebral body.

In the cases presented from our series, the earliest roentgen evidence of bone involvement was located at the anterior margins of the vertebral segments. The tendency for the intervertebral space to collapse, with partial fusion of the involved adjacent vertebra, is common. The occurrence of similar roentgenographic changes in the vertebral bodies after operative procedures of the urinary tract, especially following prostatectomy, has been noted.⁷ Transmission of infection by way of the extradural venous plexus has been stressed by Batson.² Thus, it becomes clear that when vertebral involvement occurs post-operatively, in the presence of pre-existing soft tissue infection, a causal relationship is implied.

The response of the intervertebral disk to infectious agents, chemical irritants, and primary degenerative disk disease has been studied.^{5,7} Ford and Key⁵ injected chemical agents into the canine intervertebral disk and produced reactive changes in the adjacent vertebrae. The resulting fibrotic changes and granulation tissue bridged the intervertebral disk space of the adjacent vertebra, with obliteration of the space after 15 weeks to 1 year. Roentgenographic changes in the intervertebral disk space have been observed following diskography⁶ and spinal anesthesia,¹⁰ consisting of narrowing and collapse of the vertebral interspace with lipping and hypertrophic changes involving the vertebral margins.

A variety of osseous changes may occur in the course of progressive degenerative intervertebral pathology.⁴ Extensive osteophyte formation and sclerosis have been described as a part of the disease process in the nonsurgically treated patients. However, lytic changes involving the anterior aspect of the vertebral body, and deformity

and varying degrees of interbody fusion as noted in the above cases have not been found in nonoperative cases. Clinical observations on spondylitis involving the intervertebral disk which occurred without prior surgery have been reported by Ghormley and associates.⁷ Stern and Crandall,¹³ in presenting their cases of spondylitis following disk surgery, attributed the etiology to wound infection. Though the onset of symptoms may be delayed as long as 3 months following operation, roentgenographic changes have been demonstrated as early as 8 weeks. The pain may be severe, prolonged, and simulate, to some extent, the patient's initial lumbar disk symptomatology. The discomfort is usually centered in the lumbar area, though it may be referred laterally to the flanks, lower abdomen or groin. Often, there are complaints of fullness in the region of the lower extremities. Motion of the back or lower limbs, or strain produced by coughing or sneezing, frequently initiates spasms of pain. Low grade fever, leukocytosis and elevation of the sedimentation rate may be present, though these were absent in most of our cases. Spasm of the erector spini muscles was a constant physical finding. There was a paucity of organic neurologic signs and some patients were suspected initially of having developed a functional reaction to their illness.

The lateral lumbar roentgenogram supplemented by laminagrams, provides the best opportunity to demonstrate the early changes. Initially, the epiphyseal plates adjacent to the intervertebral disk space become indistinct and lose their normal sharp outline. Gradual and progressive narrowing of the intervertebral disk space may follow, possibly proceeding to total collapse, with approximation of the vertebral bodies as proliferation of new bone occurs. Spurring around the periphery of the joint space, especially along the anterolateral aspect of the vertebral body, usually develops. These proliferative beaks of bone simulate the osteophytes found in osteoarthritis. No paravertebral soft tissue mass formation

has been recorded in any of the series of cases quoted. The subarticular sclerosis of the vertebral body is a constant finding. The narrower the vertebral interspace, the denser and wider the layer of sclerotic bone in the adjacent vertebral bodies. The end result may be firm bony interbody fusion with various degrees of obliteration of the interspace. After interbody fusion of the vertebrae has occurred, the extensive sclerotic changes recede, suggesting that motion of the 2 vertebrae in abnormal contact may have been responsible for the sclerotic reaction. Finally, a uniform density may be demonstrated in the vertebral bodies and fine vertical lines of bony trabeculation may be visualized extending from the body of one vertebra to the other across the obliterated interspace. The marginal osteophytes, seen occasionally on the anterior aspects of the interspace as a sequel to intervertebral disk surgery, are of material interest. The herniation of small fragments of intervertebral disk through the relatively thin anterior longitudinal ligament may be responsible for focal irritation and may excite localized proliferation of bone, resulting in formation of the sentinel osteophyte.

Proper immobilization of the spinal column, either by cast or rigid brace, has proved to be the treatment of choice until symptoms subside or fusion has occurred. In instances where an organism responsible for the infection is known, appropriate antimicrobial therapy is indicated. The routine use of antibiotics in cases in which a specific organism has not been isolated is not recommended. Spinal fusion for postoperative complications of the intervertebral disk space as in Case 1 may be effective.⁹ The use of steroids and radiation therapy have not been associated with any clear-cut symptomatic improvement or reversal of the roentgenographic changes seen in the spine.

CONCLUSIONS

Variable pathologic changes may occur at the intervertebral disk space following surgical removal of the herniated nucleus

pulposus. The clinical diagnosis of a continuing osseous disease process may be difficult. The most significant early roentgenographic sign of involvement is the indistinct appearance of the epiphyseal plates adjacent to the involved interspace. This finding may not be demonstrated until some weeks following operative intervention. Later, narrowing of the intervertebral disk space develops with proliferation of new bone occurring around the periphery of the joint, most notably at the anterolateral aspects of the vertebral bodies. Eventually, varying degrees of interbody fusion occur. It has been stressed that, despite the variety of causative factors, the response of the vertebral disk and the roentgenographic features are similar. The importance of obtaining serial roentgenographic studies in patients who complain of persistent lumbar pain following intervertebral disk surgery is readily apparent. While the changes described above may be noted following septic involvement, other factors such as aseptic necrosis, may produce similar roentgenographic changes. A routine postoperative roentgenographic study of the lumbar spine may be of value as a baseline study for possible future evaluation.

Robert M. Lowman, M.D.
Department of Radiology
Yale-New Haven Hospital
789 Howard Avenue
New Haven, Connecticut 06504

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MULTIPLE STRESS FRACTURES SIMULATING OSTEOMALACIA

By K. A. K. NORTH, M.R.C.P.

WELLINGTON, NEW ZEALAND

PSEUDOFRACTURES are a characteristic feature of osteomalacia. Their presence, particularly when multiple and symmetric, makes a diagnosis of osteomalacia almost certain.¹⁰ The purpose of the author is to report the case of a man with multiple symmetric pseudofractures in whom no evidence of osteomalacia could be found.

REPORT OF A CASE

J. O'Sh. was born in the north of England in 1926. He was 1 of 9 siblings and went to sea at the age of 16 years, later becoming a chef in the Merchant Navy. He subsequently settled in Wellington, New Zealand, and continued to work as a chef. At the age of 15 years he had injured his right hip when he landed heavily from a fence; otherwise, his health had been excellent. At the age of 30 years he began to notice pain and swelling of the feet aggravated by walking. He became aware of instability of the left ankle with pain and tenderness over the lateral malleolus, and began to notice pain in the groin, especially when attempting to stand up from a low chair. He was treated with analgesics, milk and calcium tablets, but obtained no relief.

Early in 1961, at the age of 35 years, roentgenograms revealed numerous undisplaced fractures and he was referred to the Medical Unit, Wellington Hospital, for further investigation. Apart from cramping pains in the muscles, especially of the legs, he denied being unwell. He had never experienced tetany and only occasionally had noticed paresthesias. His diet was reasonably normal, although he was not fond of milk or cheese. He tended to be constipated and the stools were of normal color; there were no urinary symptoms. None of his relatives have been subject to fractures.

He appeared to be a healthy well-nourished man, weighing 157 pounds and being 65½ inches tall. He was tender over the right chest where he had sustained a recent injury, and over the left lateral malleolus. Movement of the right hip was limited, especially rotation. Otherwise no abnormalities were found.

Roentgenograms showed a fracture across the 7th right rib, a fracture on the medial aspect of the left upper femur (Fig. 1), transverse undisplaced fractures of the lower ends of the left fibula and tibia (Fig. 2), and a transverse fracture of the shaft of the 3rd left metatarsal. The head of the right femur was at an angle to its neck, suggesting a previous subcapital fracture. Roentgenograms of other bones including the skull showed some reduction in bone density. He was started on calcium supplements and dianabol. Over the next 2 years further fractures were observed, first on the medial aspect of the right upper femur (Fig. 3), then on the medial aspect of the right lower femur, and later on the medial aspect of the left lower femur (Fig. 4). He was free of further trouble until May, 1965 when a fracture across the base of the 5th right metatarsal appeared. There had been no obvious trauma associated with any of these fractures and attention had been drawn to them by local pain and tenderness; although they caused him to limp, he had lost no time from work. Subsequent roentgenograms have

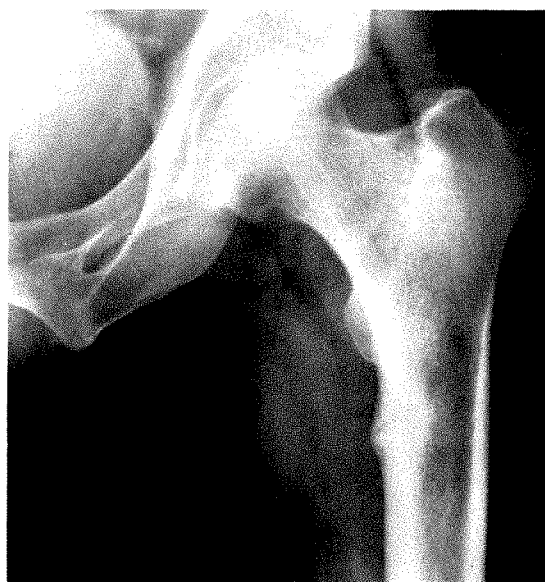


FIG. 1. April, 1961. Roentgenogram of the left upper femur showing a stress fracture on the medial side.

shown consolidation with a moderate amount of callus.

Findings. His hemoglobin was 14.4 gm./100 ml., the sedimentation rate was 6 mm./1 hr. Blood nonprotein nitrogen was 31 mg./100 ml.; serum electrolytes were normal—sodium 137 mEq/l., potassium 4.1 mEq/l., calcium 10.9 mg./100 ml., magnesium 2.2 mg./100 ml., chloride 99 mEq/l., bicarbonate 27 mEq/l., phosphorus 3.1 mg./100 ml. The serum alkaline phosphatase was 8 King-Armstrong units. Numerous estimations of serum calcium, phosphorus, and alkaline phosphatase over the period 1962–1965 have all been normal. Serum protein bound iodine was 5.7 μ g./100 ml. Urinalysis showed no abnormalities on microscopy, the pH fell to 5.2 following ammonium chloride, and chromatography showed a normal amino acid content. Creatinine clearance on a 2 hour sample was 107 ml./minute and the phosphate excretion index $+0.03$; this fell to -0.10 following a calcium infusion.⁸ After 4 days on a diet containing 150 mg. calcium, urinary excretion of calcium was 198, 250 mg. on 2 successive days. There were 12.4 mg. of 17 oxosteroids and 18.6 mg. of 17 oxogenic steroids in a 24 hour urine collection.⁹ An intravenous pyelogram was normal. An I^{131} triolein absorption test was normal. Biopsies of rib and iliac



FIG. 2. April, 1961. Roentgenogram of the left ankle showing undisplaced fractures of the tibia and fibula.



FIG. 3. December, 1961. Roentgenogram of the right upper femur.



FIG. 4. October, 1962. Roentgenogram of the left knee showing fissure fracture with callus on the medial aspect of the femur.

crest showed no obvious abnormalities; in the rib biopsy the trabeculae were considered thinner and sparser than normal but neither decalcified nor undecalcified section showed any evidence of wide osteoid seams.

DISCUSSION

When Milkman⁷ wrote the second of his papers on a case of "multiple spontaneous idiopathic symmetrical fractures," he claimed he was reporting a new disease. Controversy soon developed, however, culminating in a forceful paper by Albright *et al.*¹ who showed that all cases of Milkman's syndrome in which adequate biochemical data were available were suffering from osteomalacia, as described by Looser.⁶ Some of the confusion was caused by Camp and McCullough's paper³ reporting pseudofractures in a variety of conditions other than osteomalacia. Albright *et al.* pointed out that certain features, especially symmetry and delayed union, distinguished the pseudofractures of osteomalacia. Nevertheless, difficulties arose, as in the 4 cases which initially puzzled Dent and Hodson.⁴ Nowell *et al.*¹⁰ concluded that, if multiple pseudofractures were seen roentgenologically, the presence of osteomalacia could be presumed.

While the symmetry and multiplicity of pseudofractures in the present case suggested osteomalacia, subsequent biochemical and histologic investigations failed to confirm this. Callus formation was somewhat more marked than one would expect to see in healing Looser's zones, and the emphasis on the weight-bearing lower limbs is more in line with the lesions being stress fractures.

Stress fractures or fatigue fractures have been recognized for many years and the March fracture of metatarsals is well known. Many reports of stress fractures appeared during the second world war, and more recently, several papers describing them in athletes, ballet dancers and others have been published.^{2,5,11} The most common site has been in the metatarsals but they have also occurred in the tibia, fibula,

femur, pubis, ulna and other bones. Rarely, has more than one bone been affected in the same individual.

The patient described here is of interest because of the number and the apparently spontaneous nature of his fractures. Were he osteomalacic this would be normal enough, but as it is there is little to account for them. The somewhat reduced bone density might explain his susceptibility to the stresses and strains of everyday life, but it is not usual to find these lesions in osteoporosis. Pseudofractures have been noted in osteogenesis imperfecta³ and it may be that our patient has a variant of this condition; he lacks the usual history of fractures in childhood but a defect of bone collagen could account for the poor resilience of his bones.

SUMMARY

At the age of 35 years, a man with previous good health was found to have several pseudofractures. Further pseudofractures appeared over the next 3 years without apparent cause. The symmetry and number of these lesions suggested that he was suffering from osteomalacia but biochemical and histologic study failed to confirm this. It is concluded that a condition of "multiple spontaneous *idiopathic* symmetrical fractures" does exist.

Wellington Hospital
Wellington, New Zealand

I would like to thank Dr. I. A. M. Prior, Director of the Medical Unit, Wellington Hospital, for allowing me to investigate this patient, and Dr. G. P. G. Sim for helpful advice.

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VERTICAL FRACTURES OF THE DISTAL TIBIAL EPIPHYSIS

By WARREN L. KUMP, M.D.

MINNEAPOLIS, MINNESOTA

INTRA-EPIPHYSEAL fractures receive little attention in the widely used classifications of ankle injuries.^{2,3,5,9} Experience with 39 cases indicates that the pathogenesis of many such fractures is related to the manner in which the epiphysis unites, and sets them apart from other ankle injuries in children. The fractures referred to consist of vertical, or nearly vertical, fractures of the distal tibial epiphysis with no apparent crushing or comminution of the epiphysis.

The delicate lamellar bone adjacent to the growth cartilage is the weakest zone in the distal tibia.⁵ This accounts for the prevalence of epiphyseal separation as the most frequent serious injury to the distal tibia in children.⁷

When union of the epiphysis begins, the first replacement of the growth cartilage by trabeculated bone occurs in the medial aspect of the tibia near the junction of its medial and central thirds. This usually begins at about the age of 12 years in girls or at about 13 years in boys. In succeeding months, the process extends peripherally until union of the epiphysis is complete, usually requiring about a year and a half.⁷ This sequence of union was noted during the collection of the present series and recently has been demonstrated by Kleiger and Mankin who were able to examine the amputated tibias of a 13 year old girl and a 15 year old boy. Kleiger and Mankin, in reporting on 8 cases of fractured distal tibial epiphysis, examined 60 anteroposterior roentgenograms of ankles of normal patients ranging in age from 12 to 20 years, and observed the same manner of epiphyseal union.

Continued bone growth on the periphery of the epiphyseal cartilage after beginning of union medio-centrally centers about a local "hump" in the line of closure (Fig. 1)

and may result in some internal stresses in the epiphysis while union is proceeding.

The most significant consequence of this manner of epiphyseal union, however, is that during the phase of partial union, the medio-central zone of the epiphyseal plate is converted from a point of weakness to one of strength. The site of earliest union becomes a fixed point in the distal tibia, and any rupture of the delicate bone adjacent to the remaining growth cartilage is continued as a vertical fracture through the epiphysis rather than a displacement of the entire epiphysis.

This accounts for the tendency of vertical fractures of the lateral two-thirds of the distal tibial epiphysis to occur at the time when epiphyseal union is under way (Table 1).

CLINICAL MATERIAL

All of the 39 cases of distal tibial epiphyseal fracture were collected from the Emer-



FIG. 1. Thirteen year old boy with undisplaced vertical fracture of central third of distal tibial epiphysis. Arrow indicates the "hump" about which union of the epiphysis began. The lateral half of the epiphysis has not yet united.

gency Receiving Department and Out-Patient X-ray Department of North Memorial Hospital, Minneapolis, during a period of 7 years. During this period the departments were serving an average of 24,000 patients annually. The hospital is a private voluntary institution serving a suburban area.

Study of the 39 cases revealed that they could be divided into 3 rather distinct groups, depending on whether the fracture occurred in the lateral third, central third, or medial third of the epiphysis.

FRACTURES OF THE LATERAL THIRD

All 6 of the fractures of the lateral third of the epiphysis were fractures of the so-called anterior tibial tubercle^{4,6} (Fig. 2). This is the shallow portion of the epiphysis which lies anterior to the distal fibula. It is vulnerable to fracture because it is relatively narrow in its anteroposterior diameter and also because it is the site of insertion of the inferior tibio-fibular ligament. The separated tubercle has been compared to the intermediate fragment of Tillaux,^{4,7} which is avulsed by the same ligament in fractures of adults. Paleari,¹¹ however, believes that some of these fractures are due to direct force applied against the tibial epiphysis by the distal fibula acting as a club.

Comparison of the 6 cases falling in this

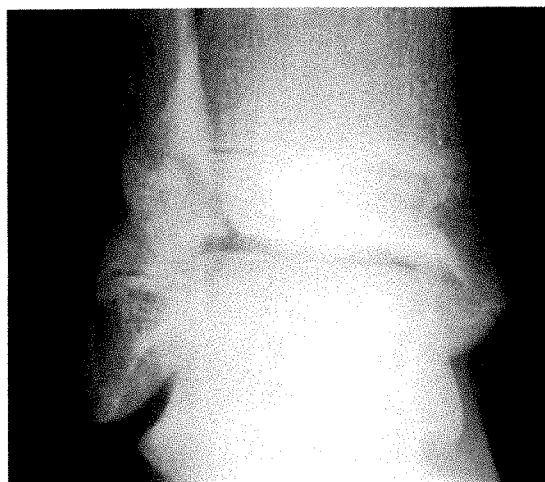


FIG. 2. Fracture of lateral third of epiphysis with minimal displacement. Separated fragment is the anterior tibial tubercle which is the shallow portion of the epiphysis lying anterior to the fibular groove.

group revealed a striking similarity, and Figure 2 is representative. Four were females and 2 were males, with ages ranging from 12 to 14 years. In each case the distal tibial epiphysis appeared to be partially united. Five were isolated fractures and 1 was associated with a metaphyseal fracture. In 2 there was no displacement, and in none was there more than a 6 mm. displacement. McWilliams¹⁰ has reported on the clinical aspects of 30 fractures of this type.

FRACTURES OF THE CENTRAL THIRD

The largest group in this series was that of fracture of the central third of the tibial epiphysis, comprising 21 fractures in 20 patients. There were 8 males and 12 females ranging in age from 12 to 16 years. In 15 of the 20 individuals, there appeared to be partial union of the epiphysis. The fractures in this group were also quite similar in appearance, and Figure 3, A-D is representative of the group. Figure 3, A-D is of special interest because it shows the only instance of vertical fracture of both distal tibial epiphyses in a single individual. This case is briefly reported.

P.M.W., was a 15 year old male who twisted his left ankle while playing football on October

TABLE I
DISTRIBUTION BY AGE AND SEX OF 27 CASES OF
FRACTURE OF THE CENTRAL AND LATERAL THIRDS
OF THE DISTAL TIBIAL EPIPHYSIS

			○			
		○	○			
		○	○	○		
		○	○	○		
		○	○	○	×	
		○	○	○	×	×
	○	○	○	○	×	×
Age (yr.)	11	12	13	14	15	16

X = males.

O = females.

Note similarity to incidence of beginning epiphyseal union. As would be expected, the peak incidence in females precedes that in males.

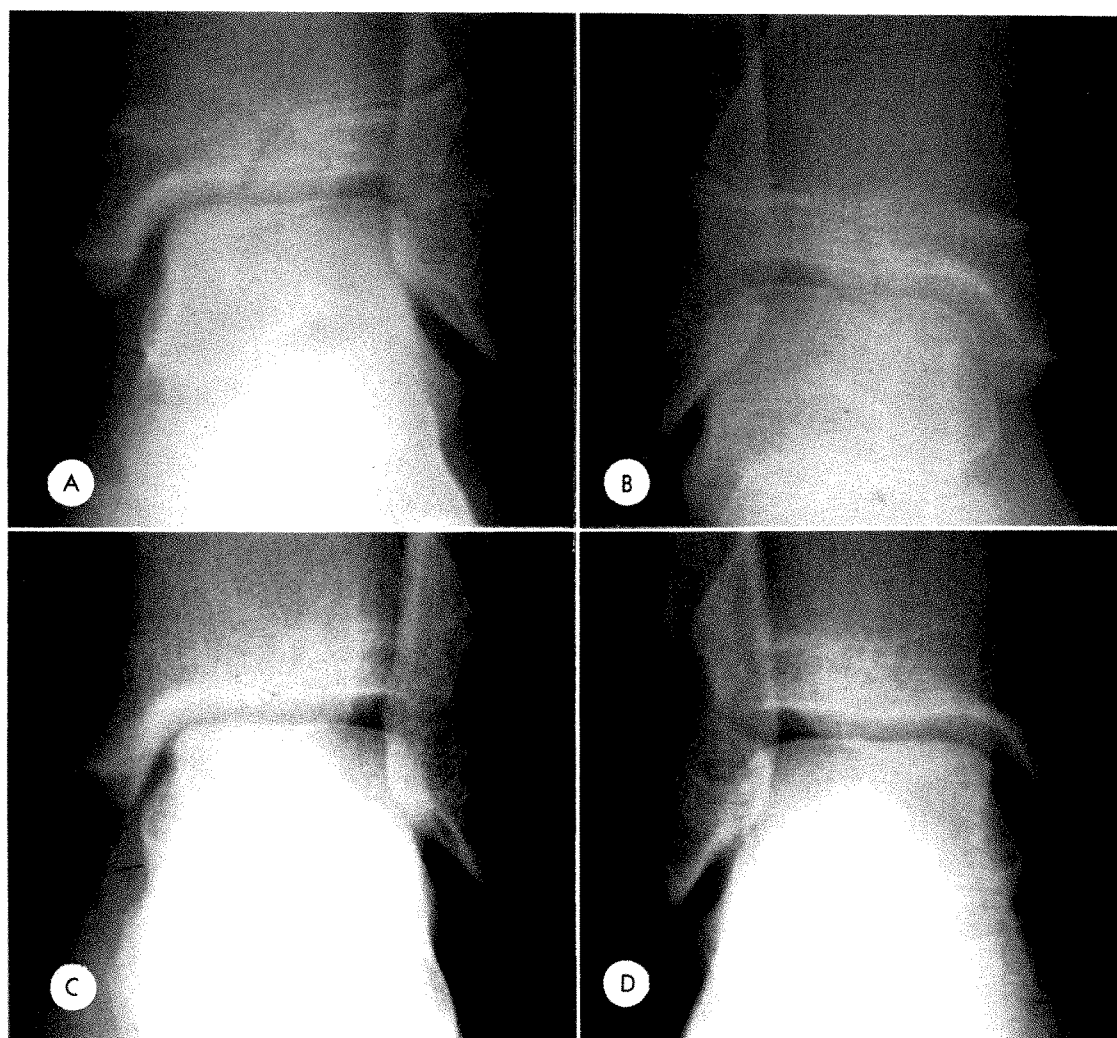


FIG. 3. Fifteen year old boy. (A) Undisplaced fracture of central third of left tibial epiphysis on October 13, 1963. (B) Similar fracture of right tibia a month later. Note that only the medial portions of the epiphyses are united. (C and D) One year later. Both fractures are healed and the epiphyses solidly united. Ankles subjectively and objectively normal.

13, 1963. He was seen in Emergency Receiving 3 hours later, unable to bear weight on the ankle. Physical examination revealed moderate soft tissue swelling over the medial malleolus and pain on tibio-fibular compression. Roentgenograms demonstrated a joint effusion and an undisplaced slightly oblique fracture of the central third of the tibial epiphysis (Fig. 3A). There was evidence of partial union of the epiphysis.

The ankle was immobilized in a plaster cast for 3 weeks, at which time there was evidence of early healing. Limited weight bearing was begun.

Twelve days later on November 16, 1963 he stepped into a hole and injured the right ankle. At Emergency Receiving, pain and swelling were noted just anterior to the lateral malleolus, and movement of the ankle was painful. Roentgenograms demonstrated a fracture (Fig. 3B) remarkably similar to that which had occurred in the other ankle slightly more than a month earlier. This fracture was also treated simply with immobilization in plaster.

He was examined 1 year later, at which time both ankles were free of pain and showed a normal range of motion. Roentgenograms at that time revealed the fractures completely

sively larger. Eventually, the cortex may break and cause a pathologic fracture. As the pathologic fracture attempts to heal, or as the granulomatous process separates the periosteum from the cortex, formation of new bone may be seen roentgenographically, as "periosteal reaction" adjacent to the abnormal cortex. Progression of lesions is usually slow but may be rapid.¹¹ Lesions in specific bones may have certain features worthy of note.

Skull. One-third of our patients had cranial granulomas. The eosinophilic granuloma produces a clearly defined area of radiolucency, usually with a sharp border and involving both the inner and outer tables of the bone. A "bevelled edge" may be found. There is neither sclerosis of the border of the defect nor adjacent hyperostosis or cortical thickening. Meningeal or periosteal calcification was not seen in any of our patients. Vascularity of the surrounding skull was normal. None of the defects showed the peculiar granularity that is sometimes seen in hemangiomas. Only one showed the central "button of bone" that Wells¹⁸ reported in several eosinophilic granulomas, and it is interesting that this disappeared in the 6 month interval between initial recognition and final proof by local resection (Fig. 1, *A* and *B*).

Mastoid. Eosinophilic granulomas of the mastoid do not present a specific roentgenographic appearance. A radiolucent area appears in the bone. Clinical as well as radiologic diagnosis is likely to be cholesteatoma, which presents the same general appearance and is more common. Two of our patients had this type of lesion, one a solitary lesion and the other secondary involvement several years after a mandibular lesion had disappeared after radiation therapy.

Mandible. A relatively large, fairly well defined, radiolucent area may develop in the mandible. A 4 year old boy in our series had such an eosinophilic granuloma, involving the horizontal ramus and producing a "cyst-like area," in which one of the teeth seemed to be almost floating. The

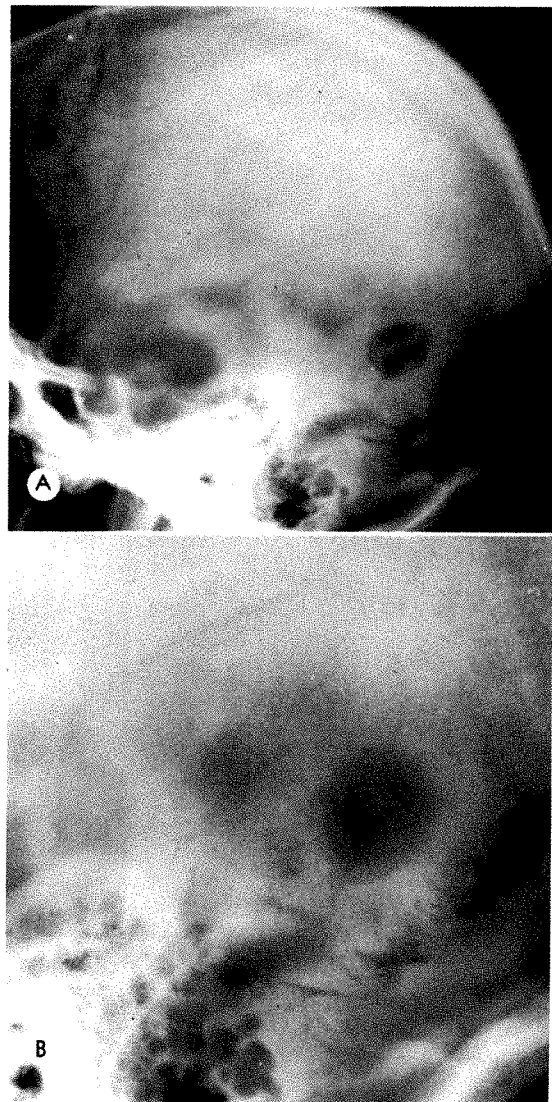


FIG. 1. (*A*) Roentgenogram of skull shows well defined radiolucent lesion in parietal bone. (*B*) Central opaque button disappeared in 6 months, but note bevelled edge of lesion.

lesion disappeared after radiation therapy and the bone was so completely reconstituted that it appeared normal on subsequent roentgenograms (Fig. 2, *A* and *B*).

Spine. The roentgenographic appearance of vertebrae affected by eosinophilic granulomas comes closer to being pathognomonic than any other roentgenographic manifestation of the disease. The vertebral body is generally affected, loses some of its



FIG. 2. (A) Eosinophilic granuloma of mandible before treatment, and (B) 2 years after biopsy and radiation therapy (600 r).

structural bony strength, and collapses to some degree. Vertebra plana is the result. Flattening may be extreme and only a thin wafer of bone remains. It is usually denser, and therefore whiter, in the roentgenogram than the adjacent vertebra (Fig. 3). These granulomas may occur in any portion of the spine and usually a single vertebra is affected. In discussing Compere and co-workers'⁴ statement that vertebra plana is characteristic in eosinophilic granuloma, Hillman pointed out that it is not pathognomonic and he showed a roentgenogram

of a characteristic vertebra plana which developed within 1 month in a boy with sarcoma of bone.



FIG. 3. Vertebra plana of cervical spine due to eosinophilic granuloma.



FIG. 4. Localized osteolytic tumor in rib which proved to be an eosinophilic granuloma.

healed and the epiphyses united (Fig. 3, *C* and *D*).

The case of P.M.W. is similar to the others in this group in that 15 of the 21 epiphyseal fractures were not associated with any other fracture of the ankle. In the remaining 6, there were fractures of the metaphysis of the tibia in 4, of the distal fibula in 3, and of the medial malleolus in 1.

There was no displacement in 12 cases and, of the remaining 9, the greatest displacement was a 5 mm. posterior shift of

the separated lateral fragment.

As might be expected, the cases showing displacement tended to be the same ones in which more than one fracture occurred.

FRACTURES OF THE MEDIAL THIRD

This group included 12 cases, and was the most heterogeneous of the 3, both in the appearance of the fractures and in their age incidence. The patients varied in age from 5 years to 16 in a random fashion (Table II). Only 5 of the 12 showed evidence of partial union of the epiphysis. Ten of the 12 fractures were not associated with any

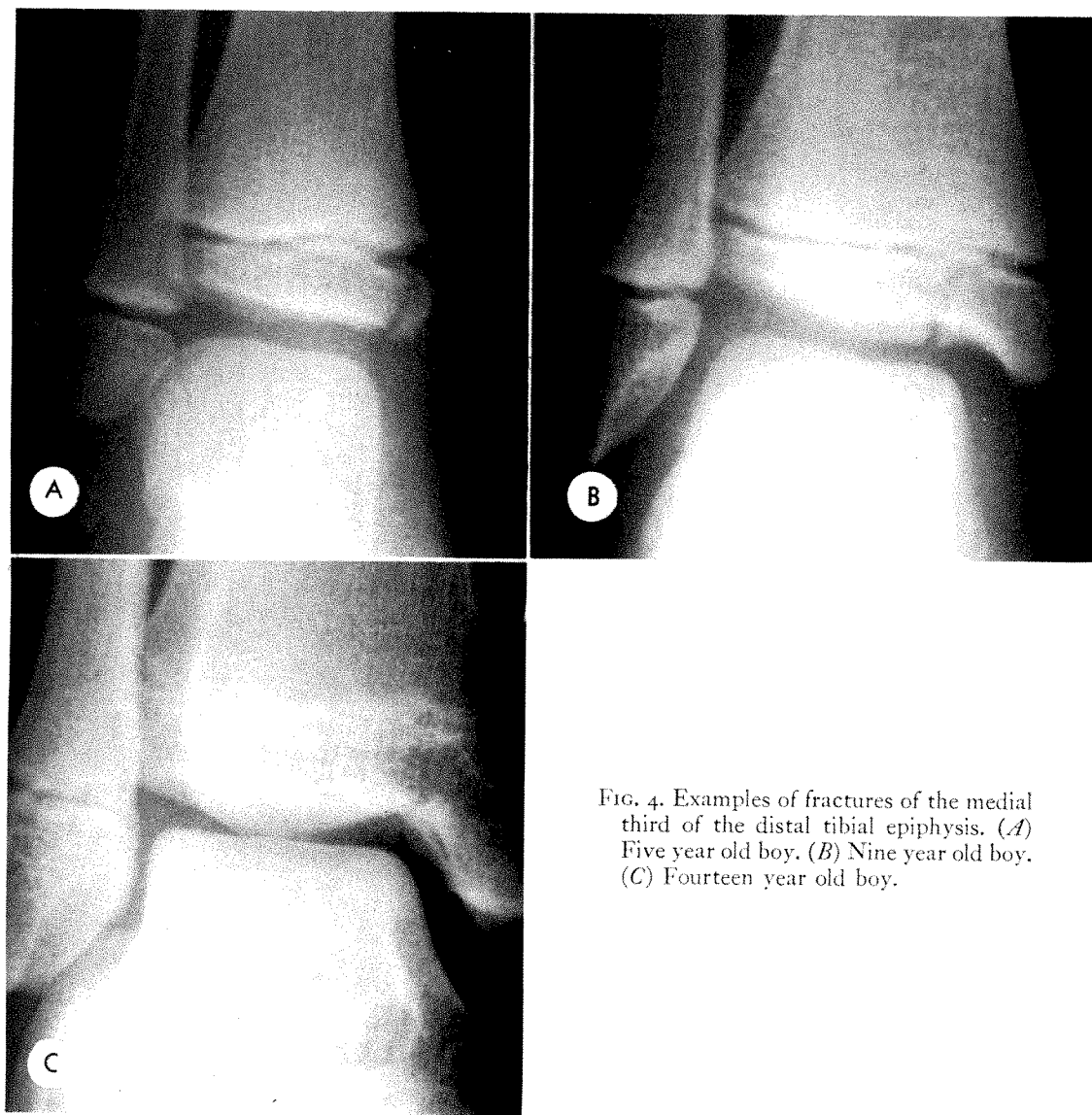


FIG. 4. Examples of fractures of the medial third of the distal tibial epiphysis. (*A*) Five year old boy. (*B*) Nine year old boy. (*C*) Fourteen year old boy.

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BONE CHANGES FOLLOWING ELECTRICAL INJURY*

CASE REPORT AND REVIEW OF LITERATURE

By LOUIS B. BRINN, M.D., and JOHN E. MOSELEY, M.D.

NEW YORK, NEW YORK

RECENTLY, the authors reviewed the roentgenograms of a man who had suffered an electrical injury in industry. As we were without personal experience in such cases, the pertinent medical literature was reviewed. The survey revealed, somewhat to our surprise, an almost complete lack of English language articles dealing with the roentgenologic changes which may follow electrical injury. In the last decade, almost all articles have been in German, Italian, Russian or various Eastern European languages. There are probably several factors responsible for the absence of discussion of this subject in the English language literature. Firstly, industrial safety measures in the United States help keep the incidence of electrical injuries low. Secondly, and probably most important, any one radiologist or any one hospital in the United States is likely to have a very limited experience with these cases. On the other hand, in Middle and Eastern Europe there is a tendency to send electrical injury cases to a few large, specialized institutions where considerable experience with such cases may be acquired. Thirdly, due to a lack of knowledge regarding the nature and extent of possible injury due to electrical current, many cases are not examined roentgenographically, are not given adequate clinical examinations and are not followed-up. The following case illustrates interesting bone changes which were not suspected on initial clinical examination.

REPORT OF A CASE

The patient was a 60 year old male, who, on October 9, 1953 in Pittsburgh, Pennsylvania, sustained a severe electrical injury while at work. The patient touched two metallic parts, one with each hand, which were in a 2,500 volt circuit. The current evidently passed from one

hand to the other. He did not lose consciousness during the accident but could not release the metal parts until the switch was thrown after 15 to 20 seconds. No artificial respiration was required. The patient showed no evidence of central nervous system injury. The main finding on physical examination was a massive bilateral, hemorrhagic swelling involving both shoulder regions and both upper arms. The patient also had severe limitation of movement of the shoulders. It was felt that the findings were due to internal burns. Fracture was not suspected and no roentgenograms were taken at the time.

Ultimately, in February, 1955, about 1½ years after the accident, roentgenograms were taken elsewhere and are said to have shown bilateral humeral fractures.

In May, 1955, the patient was seen by an attending physician of The Mount Sinai Hospital, New York (Dr. M. Yohalem), who noted that both shoulders had severe limitation of motion. The upper arms were deformed, particularly the right arm which was shortened. Roentgenograms at The Mount Sinai Hospital showed bilateral fracture dislocations of the shoulders, more marked on the right. On the right, there was a comminuted fracture at the junction of the head and shaft of the humerus with a large bone fragment displaced medially. The fracture fragments were widely separated and there was a remarkable mottled decalcification of the humeral head as well as of the separated fragment. The cortex of the shaft of the humerus was thin. The shaft and lower portion of the humerus were decalcified with discrete areas of more marked rarefaction. There were also fairly well demarcated, elongated areas of rarefaction in the upper portion of the shaft of the right radius. On the left, there appeared to have been less comminution, and old fracture lines were not clearly visible. There was a large bone fragment extending horizontally from the region of the neck of the humerus toward the glenoid which apparently represented a deformed humeral head. Changes similar to those on the right side were noted in the shafts of

* From the Department of Radiology, The Mount Sinai Hospital, New York, New York.



FIG. 1. Comminuted fracture dislocation of the right shoulder. Comminuted fracture at the junction of the head and shaft of the humerus with a large bone fragment displaced medially. There is mottled decalcification of the humeral head. The cortex of the humerus is thin. The medullary cavity is widened and discrete areas of rarefaction can be seen in the shaft and distal metaphyseal region.

the left humerus and radius. No treatment was given to the patient other than physiotherapy.

PATHOLOGY AND PATHOPHYSIOLOGY

There are many factors which determine the effects of an electric current on an organism.^{2,5,8,9,10,12} The principal ones may be listed as follows: (1) type of current (AC current is 3 or 4 times as dangerous as DC); (2) voltage; (3) amperage; (4) duration of contact with the electrical current; (5) path taken by the current in the body; (6) resistance at the point of contact and elsewhere in the body; (7) points of entrance and exit; (8) atmospheric conditions; and (9)

factors related to the individual's state of general health.

Death from low voltage electrical injury, especially below 220 volts, is usually due to ventricular fibrillation,¹⁰ while above 1,000 volts it is due to the inhibition of the central nervous system respiratory center.^{2,9,10} In certain cases, tetanic spasm of the respiratory muscles may contribute to the death of the individual.

Tissue temperatures during electrical accidents can momentarily reach several thousand degrees centigrade,^{2,8,9} and this can cause heat necrosis of bone or full thickness skin loss. Tissue death can occur with coagulation of protein and liquefaction of fat. The protein and fat of muscle, blood and connective tissue are particularly susceptible. The intense heat can also vaporize water in the tissues and cause carbonization of organic matter.⁵

Electrical injury may result in cell death or may alter cellular activity, either temporarily or permanently. The current can affect conductivity of nerve trunks, motor activity usually failing before sensory activity. There may be progressive central nervous system or peripheral nerve damage leading to paralysis, sensory disturbances, or vasomotor phenomena. Late neurotrophic changes may develop.⁵ In the long run, after electrical injuries, there may be vascular disturbances with progressive vessel thrombosis, as well as weakness and fragility of blood vessel walls. Edema from lymphatic or venous obstruction can occur. Tissue repair after electrical accidents is often poor. In general, the tissues offering the greatest resistance to the electric current suffer the greatest damage.

Bone changes after electrical injury can result from several possible mechanisms, some of which are not well understood. The authors feel that the heat associated with the passage of the current is responsible for some changes. Mechanical trauma is, at times, involved either as external trauma or from uncoordinated muscle spasms. There also appears to be a specific "electrical" effect independent of the thermal and



FIG. 2. Comminuted fracture dislocation of the left shoulder. There was apparently less comminution than on the right side. There is a bone fragment projecting horizontally from the region of the neck of the humerus toward the glenoid. This apparently represents the deformed head of the humerus. The cortex of the humerus is thin and the medullary cavity is widened. Some areas of discrete rarefaction are noted in the lower end of the shaft.

mechanical factors. Associated soft tissue injury, neurologic damage, blood vessel damage, infection and disuse all may produce changes in bone. Much more basic research is needed before there is an intelligent understanding of the modifications in osseous structure and physiology resulting from electrical trauma. One example of such basic research is the study of Granberry and Janes,³ where an attempt was made to influence bone growth by stimulating the epiphyseal plates of bones in dogs with implanted electrodes. (In their par-

ticular study, no acceleration of growth occurred with electrical stimulation.)

ROENTGEN FINDINGS

Some of the roentgen findings associated with electrical accidents are due to associated mechanical trauma. Certain of the mechanical traumas are external in nature, as for example, when someone receives an electrical shock, falls to the ground, and sustains a fracture secondary to the fall. Another group of mechanical injuries results from uncoordinated muscle spasms secondary to the irritating effect of the current on nerves and muscles. Dislocations of the joints can occur, as can avulsion fractures. Compression fractures of the vertebrae result from spasmodic contractions of the trunk muscles. These are produced by the same mechanism as the fractures which occur in electroshock therapy. Fractures and fracture dislocations of the

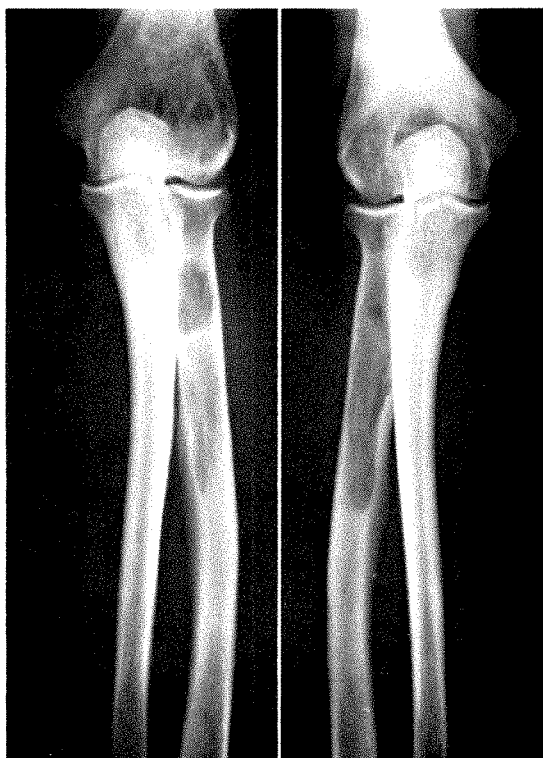


FIG. 3. View of both forearms. There are well demarcated, elongated areas of rarefaction in the upper portion of the shafts of both radii.

humerus, fractures of the scapula, and fractures of the forearm have all been noted.⁸

Roentgen changes also apparently may result from the thermal effect of current. Small rounded densities resembling "bone pearls" or even "wax drippings" have been noted,⁸ and it has been theorized that these may be secondary to actual melting of bone by the intense heat. The severe heat may cause disintegration of an entire bone or part of it; it may cause charring of bone leading to bone necrosis. The resulting bone necrosis roentgenologically is similar to necrosis from other etiologies. The surrounding soft tissues may be charred leading to chronic changes such as tissue contractures, joint contractures, joint dislocations and demineralization of the regional bone. Schinz *et al.*¹¹ feel that the late roentgenograms after electrical injury can resemble those seen after serious burns, with joint contractures, severe demineralization of adjacent skeletal parts and mutilating elimination of necrotic bone particles. Immobilization, soft tissue deformities, vascular injuries and neurologic injuries are all involved in producing the roentgen findings in addition to direct injury to bone by the electric current.

Jellinek⁶ and others have observed fine disruptions of bone continuity after electrical accidents. Jellinek⁶ in an early article described these fine fractures in great detail. He felt these were due to the effects of the electrical current, quite possibly from the heat produced. Schinz *et al.*¹¹ quote Jellinek as stating that the fine fractures are due to evaporation of fluid caused by the severe heat which is generated. Kolar and Vrabec⁸ quote Jenny as also stating that evaporation of bone fluid causes overpressure in the bone resulting in fine fracture lines. These fractures may be very delicate, short in length and difficult to visualize on initial roentgen examination, requiring multiple views or even follow-up examinations.

Review of the literature also revealed a wide variety of unusual findings reported

by scattered authors, some of which will be mentioned below. Acro-osteolysis of the distal phalanges of the toes has been reported;⁸ Kolar and Vrabec feel that these findings are likely secondary to trophic changes rather than to a direct electrical effect on bone. Periosteal reaction has been described by several authors. Freyer¹ noted periosteal reaction and also quotes Jellinek and Palugyay as having seen it, the latter feeling that periosteal reaction tends to occur in children and not in those past puberty.

Kolar and Vrabec,⁸ in their extremely comprehensive article described swelling of bone, in certain cases resembling the so-called "spina ventosa" of inflammatory origin. These same authors⁸ described 2 interesting cases of osteochondritis, one in the head of the second metatarsal and the other in the metacarpal bone of the thumb. These are apparently the only reported cases secondary to electrical injury.

Joint changes are often seen accompanying soft tissue injuries from electrical accidents. The latter may cause contracture deformities, limitation of joint motion and even subluxation. Joint infection may occur and lead to ankylosis. Periarticular calcification and even periarticular bone formation can occur.

Children may show the same changes as adults, but also have abnormalities of growth secondary to the effect of the current on the epiphyseal cartilage. The epiphyseal center and the epiphyseal cartilage may both be affected by the current, and there may be remodeling of the metaphyseal region.⁸ Three cases are reported in which electrical accidents resulted in extensive soft tissue burns requiring amputation of phalanges. In these cases, several of the remaining phalanges showed an abnormal elongation. This overgrowth could be secondary to chronic hyperemia resulting from the extensive soft tissue injuries, with infection contributing to the hyperemia as well.

Our case showed several interesting roentgen findings, namely, fracture disloca-

tions of both shoulders, mottled decalcification in the humeri, thinning of the cortices and widening of the medullary cavities in both humeri, and discrete areas of rarefaction in the humeri and to an even more striking degree in both radii. The fracture dislocations were apparently caused by severe, uncoordinated muscle spasms as has been reported in the literature. The mottled decalcification is mainly due to disuse; hyperemia secondary to fracture and to soft tissue injury probably played a very important part as well in the more immediate post-accident period. We have no explanation for the widening of the medullary cavities with cortical thinning in both humeri. To our knowledge, these findings have never been reported in association with electrical injuries. The discrete areas of rarefaction in the humeri and radii are also difficult to explain. Other authors⁸ have reported lucent "holes" in bone after electrical injury, these holes apparently remaining permanently rather than disappearing with time. No explanation was offered for the lucent holes. The areas of rarefaction in our case are quite well defined and particularly in the radii are a very striking finding. They certainly do not appear to represent the usual pattern of osteoporosis after fracture, soft tissue injury and disuse. More pathologic and physiologic studies will be needed before a more knowledgeable analysis of the roentgen findings can be made.

SUMMARY

A case of bilateral fracture dislocations of the humeri secondary to electrical injury is presented. The literature on roentgen changes after electrical accidents has been reviewed. The chief purpose of the paper is to acquaint the American radiologist with

the variety of bone changes which may be found in association with electrical injury.

Louis B. Brinn, M.D.
Department of Radiology
The Mount Sinai Hospital
100th Street and Madison Avenue
New York, New York

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NONINFECTIOUS SYMPHYSIAL BRIDGING AND PSEUDO-MARSUPIAL BONES*

By GOTTWALD SCHWARZ, M.D.,† and GERHART S. SCHWARZ, M.D.
NEW YORK, NEW YORK

IN 1950, my father, the late Dr. Gottwald Schwarz, asked me to collaborate with him on a study of symphyseal bridging. He supplied me with roentgenograms of such a case (Case 1 of this series) collected in his private office. This happened shortly after I had joined the X-ray Department of the Presbyterian Hospital of New York, then headed by Dr. Ross Golden. Dr. Golden thereupon made the files of his department available to my father and myself and with his permission, I began collecting new cases as I came upon them during routine reporting. After the retirement of Dr. Golden in 1955, my activities turned from the contemplative collecting of cases into experimental research, and thus I shelved the project until 1964. My present position at the New York Medical College Center for Chronic Disease, Bird S. Coler Hospital, confronted me with abundant suitable clinical material, and enabled me to bring the series to a speedy conclusion.

Bridging of the pubic symphysis is occasionally observed on roentgenograms of the abdomen and the bladder region. The most common type consists of an osseous spur that arises from the superior margin of one pubic bone, crosses the midline and either attaches to the superior margin of the opposite pubic bone or forms a roof over it without exhibiting any signs of attachment or fusion (see Case 1 below).

However, there appears to be a greater variety of symphyseal bridges which reflect diverse etiologies. In the series of cases presented here, the following etiologies may be considered (some of which were proven by history, subsequent events or biopsy, whereas others are conjectures): (1) degenerative; (2) traumatic; (3) surgical; (4)

Marie Strümpell spondylitis; and (5) myositis ossificans. The purpose of this paper is to present illustrative examples of these conditions and consider the congenital or developmental anomalies in the differential diagnosis.

Excluded from this series are all cases in which the bridging followed an infectious process such as osteitis pubis, osteomyelitis or tuberculosis. On a purely descriptive basis, the roentgenographic appearance of noninfectious symphyseal bridging can also be classified as follows: suprapubic—complete (symmetric and asymmetric) and incomplete; intrapubic; infrapubic; complete osseous union; and suprapubic ossification resembling marsupial bones.

REPORT OF CASES

CASE 1. *Complete asymmetric superior symphyseal bridging.* M.F., a 76 year old white male, submitted to intravenous pyelography for evaluation of benign prostatic hypertrophy. The pyelogram showed no urinary abnormality except for an enlargement of the prostate. However, as an incidental finding, an asymmetric osseous bridge was noted which seemed to arise from a broad base on the superior margin of the

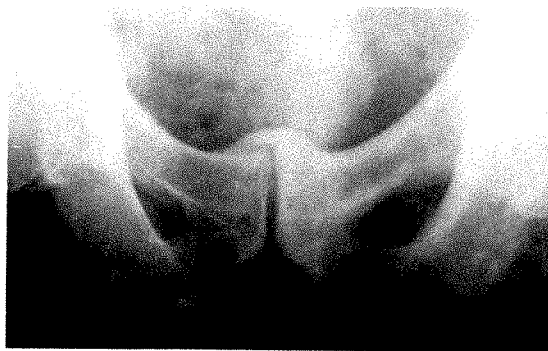


FIG. 1. Case 1. Degenerative bridging.

* From the Radiology Service, New York Medical College Center for Chronic Disease, Bird S. Coler Hospital, Welfare Island, New York, New York.

† Honorary member of the American Roentgen Ray Society (Deceased 1959).

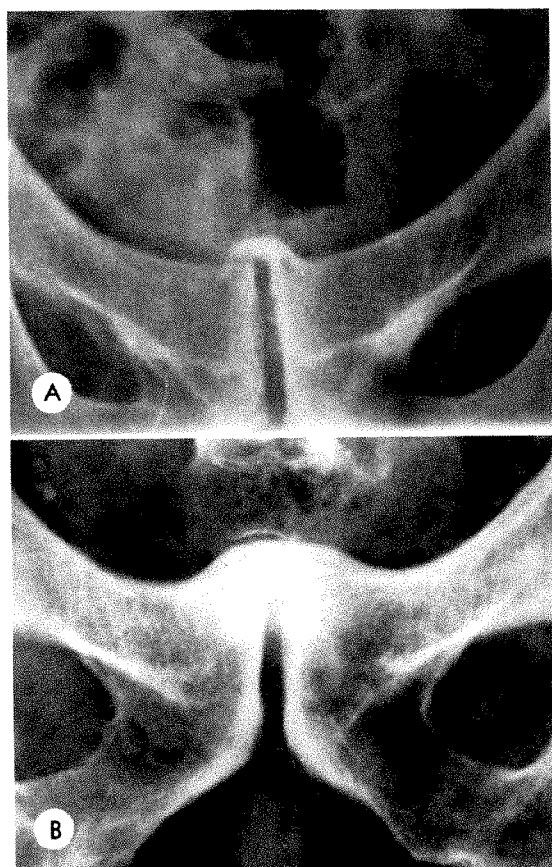


FIG. 2. (A and B) Degenerative bridging.

left pubic bone and fused with the superior margin of the right pubic bone. It was curved (Fig. 1), its convexity pointing in the cephalad direction. It measured 3 cm. in length on the roentgenograms. Its broad base measured 16 mm. in width, whereas its apex measured only 5 mm. in diameter at the point of fusion with the right pubic bone.

There were mild pagetoid changes in the left pubic and left ischial bone. The sacroiliac joint and the lumbar spine of this patient appeared normal. They were free of osteoarthritic changes.

Comment. One is inclined to consider osteoarthritis as the etiology in this case although it is difficult to explain why the sacroiliac joints and the lumbar spine were free of roentgenologic signs of osteoarthritis here. According to Foerster³ only 3 such cases had been reported up to 1950. At the New York Medical College Center for

Chronic Disease, such hook-shaped bridges were found frequently in elderly individuals. The variety of this type of bridging is remarkable (Fig. 2, A and B). In some instances, the bridge is complete, in some incomplete, in some it assumes a hook-shaped prominence of bone, in others a garland type osseous connection. Characteristic of all these is the avoidance of the pubic synchondrosis. The osseous bridge-like structure bulges either upward or forward, and ossification of the pubic synchondrosis proper does not occur in these cases. Its incidence at the New York Medical College Center for Chronic Disease is estimated as 1 in 500 individuals, *i.e.*, 1 in 250 male patients, since it has only been found in males.*

CASE II. Spontaneous post-traumatic fusion of the pubic symphysis. Mr. G.McE., a 57 year old veterinary surgeon, had lived in India and Mesopotamia. He had sustained numerous falls from horses and one injury while playing football. He recalled the following fractures: right distal tibia and fibula, 1915; pelvis, 1918; right clavicle, 1922; right Colles' fracture 1922; and right scapula, 1939.

The physical examination was not contributory except for evidence of obesity. The blood pressure was 160/100, erythrocyte sedimentation rate 10 mm./hr., blood cell count normal.

The principal findings were those demonstrated roentgenographically: severe cystic degenerative arthritis of both hips and severe osteoarthritis of the spine. The pubic symphysis (Fig. 3) appeared to be fused solidly. A Judet arthroplasty of the right hip was performed which enabled him to walk in a limited fashion.

Comment. The ossification here was not a supra- but an intra-pubic one. In this, the roentgenologic appearance of the symphyseal synostosis differs from that in the former case. The fact that the patient suffered from demonstrable osteoarthritis in other regions of his body raises the question of a degenerative etiology; however, in view of the fact that he has sustained various frac-

* This hospital has a relatively stable patient population of 1,800-2,000, with both sexes equally represented. The average length of stay is 3 years for discharged patients and up to 12 years for the permanent ones. Their ages range from 6 to 103 years, with the majority between 50 and 90 years.

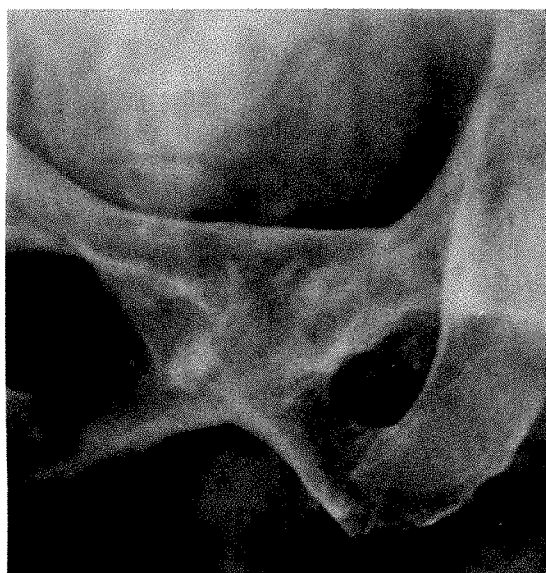


FIG. 3. Case II. Post-traumatic fusion.

tures including one of the pelvis, it is difficult to discard trauma here as the cause.

CASE III. Spontaneous traumatic fusion after fracture. S.S., a 37 year old male, was admitted to the New York Medical College Center for Chronic Disease on November 17, 1958, for paraplegia secondary to a fracture of the twelfth dorsal vertebra. He had fallen from a third story window on June 18, 1958, sustaining fractures of T-12 and L-1, and a disruption of the pubic symphysis. A laminectomy was performed the same day in another hospital, but during the ensuing months an infection of the bladder with formation of a scrotal abscess and a fistula at the dorsal aspect of the urethra developed. A cystostomy with Foley drainage was applied thereafter. During his present hospitalization, he was plagued by recurring orchitis, epididymitis and cystitis. A laboratory diagnosis of *Schistosoma mansoni* was made once on the basis of a left testicular biopsy but could not be confirmed subsequently. An ileal conduit was established on June 14, 1965, because of bilateral vesicoureteral reflux.

Roentgenograms (Fig. 4) showed a marked asymmetry of the pelvis. The right half of the pelvis had been dislocated in the cephalad direction with the result that the left pubic bone lay essentially caudad to the right one.

The interspace between the two is now bridged by an osseous structure measuring approximately 3.5 cm. in length and 2 cm. in width.

The basic dislocation that caused the shearing pubic separation occurred at the right sacroiliac joint.

Comment. One might safely assume that the etiologic factor is the same as that in Case II. This case, however, differs from the former in that the traumatic history was more decisive and osteoarthritic changes were lacking, whereas they were present in Case II in many pelvic and extrapelvic joints. Although local infection of the bladder and testes developed, there was nothing to indicate that there was involvement of the symphysis.

CASE IV. Surgical fusion. Mrs. L.E., 72 years old, had had 3 normal deliveries and one miscarriage. Her last child was born when she was 40 years of age in 1920, complicated by a difficult high forceps delivery. No symphysiotomy or injury to the pelvis was recalled. A few years later, she noticed pain in the region of the pubic symphysis when stooping forward but not when walking. Finally, the pain became so severe that a bone chip fusion of the pubic symphysis was performed in 1935. This afforded complete relief of symptoms, and she remained well in regards to this complaint up to the time her case was reviewed. Roentgenograms made on January 23, 1952 (Fig. 5) showed a complete osseous fusion somewhat resembling that in Case II. However, the ossification extended in the cephalad direction beyond the superior margin of both pubic bones by approximately 6 mm. In this case not only intra- but also a



FIG. 4. Case III. Post-traumatic fusion.



FIG. 5. Case IV. Surgical fusion.

supra-pubic ossification was present. It is reasonable to assume that the periosteum was lifted during the surgical procedure and caused bone to fill in the space created thereby. Also, the roentgenographic appearance of the symphyseal synostosis differed from that in Case II by the fact that the synostosis was less radiopaque than the pubic bones proper. Because of this, the former gap that had existed between the two pubic bones and measured approximately 1.5–2 cm. could still be identified.

Comment. One would not expect every surgical fusion to present this pattern, but it is reasonable to assume that sparsely packed bone chips fuse into an osseous structure which is less dense than the original bone. Also, not every surgical fusion bridges as large a gap between the two pubic bones as existed here. If surgical fusion were performed in a pubic symphysis which possessed a narrow cleft, this pattern would not develop.

CASE V. Rheumatoid ankylosis of pubic symphysis. F.J.G., a 26 year old former pilot, developed progressive ankylosis of practically all joints of the body. He was well until 6 years prior to admission when he sprained a muscle on a cross country run, which produced a limp. Within a year his spine became so stiff that he required help on arising. For the past two years, he was confined to bed completely. Malaise and weight loss were associated complaints. His physical examination revealed dystrophic nails and limitation of motion not only of the spine but of most peripheral joints, including the temporomandibular articulations. The phosphorus, the alkaline phosphatase and the acid phosphatase levels, as well as the calcium and

the nonprotein nitrogen levels were normal. The streptococcus A agglutination was negative and the erythrocyte sedimentation rate 44 mm./hour. Roentgenograms demonstrated a severe ankylosing spondylitis involving all sections of the spine. Similar ankylotic changes were found in both hip joints. The pubic symphysis (Fig. 6) showed fusion of its lower half. In short, the bridging here was essentially an inferior one in contradistinction to Case I in which the bridge lay at the superior margin of the symphyseal cleft. In keeping with the inflammatory nature of this process, the ankylosis progressed (Fig. 7) within a year. The pubic symphysis was still not completely closed at the time of the second roentgenographic study.

Comment. The symphyseal bridging in this case was apparently the result of severe rheumatoid arthritis. A histologic examination of tissues removed from the hip joints

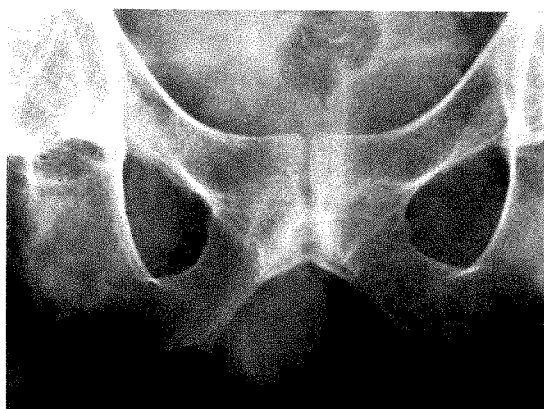


FIG. 6. Case v. Inferior bridging in Marie-Strümpell spondylitis.

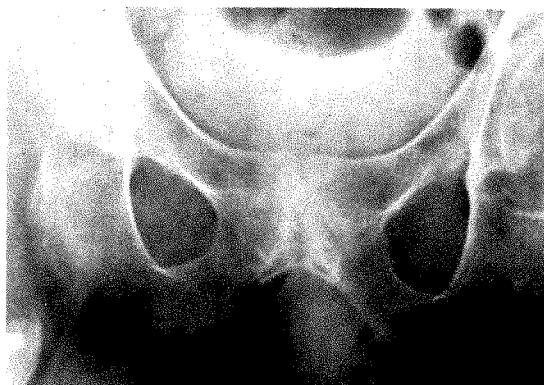


FIG. 7. Case v. One year later.

confirmed the diagnosis of rheumatoid arthritis—at least in the operative area.

CASE VI. Formation of pseudo-marsupial bones. Mrs. B.D., a 76 year old housewife, was admitted to Presbyterian Hospital for hypertension, cardiovascular disease of 7 years' duration, and arteriosclerotic heart disease. Seven months prior to the admission, a carcinoma of the left breast with axillary metastases was discovered. This had been treated non-surgically with 15 mg./day of stilbesterol for the past 4 months with a resultant decrease of the masses. Her present hospital stay was occasioned by the development of left lower quadrant pain, nausea and diarrhea. The phosphorus and alkaline phosphatase levels were normal. A skeletal survey was unremarkable.

Roentgenograms of the abdomen showed as an incidental finding peculiar osseous structures in the immediate suprapubic area (Fig. 8 and 9). A triangular structure seemed to rest upon the superior rim of the pubic cleft. From it, two oblique osseous structures arose and pointed ventrally and in the cephalad direction. They appeared to be embedded in the abdominal wall (Fig. 9). An ovoid shaped calcification projected into the symphyseal cleft. This could not be identified on the lateral view, but stereoscopy of the frontal view placed it adjacent to the anterior margin of the symphysis, resembling somewhat the os interpubale of certain animals. A calcified uterine fibroid was seen within the pelvis and was considered incidental.

The triangular structure measured 2.5 cm. in length, whereas each "ramus" resembling a

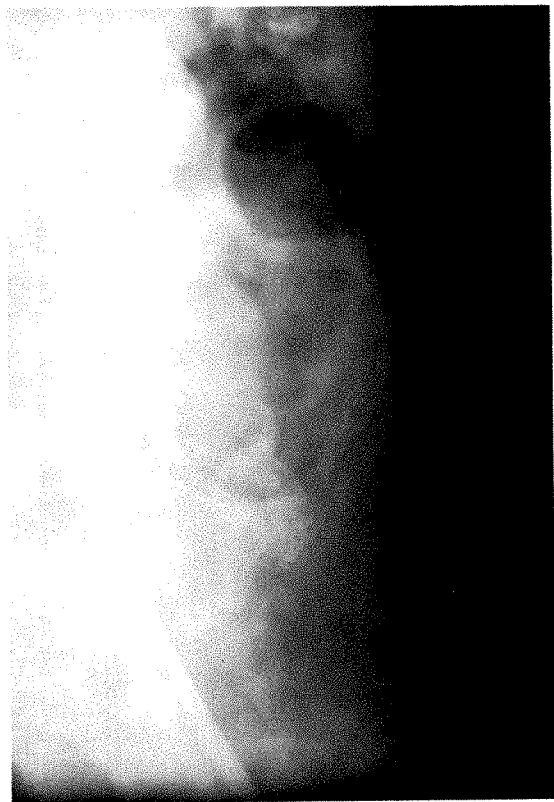


FIG. 9. Case VI. Lateral roentgenogram.

marsupial bone measured 3 cm. in length. These two "rami" were linked with the triangular base by a pseudo-articulation.

Comment. The patient did not recall any injury and had no discomfort in the region of the abdominal wall. Nevertheless, one cannot help interpreting the finding as myositis ossificans involving either the rectus or the oblique abdominal muscles. True marsupial bones have never been reported in humans, and it is unlikely that they can occur. Huxley, however, felt that rudimentary marsupial bones exist in canines. Various osseous and cartilaginous structures also exist in lower animals which resemble the structures here described, but their similarity is most likely incidental. One of these is the ypsiloid cartilage, a structure which extends from the superior rim of the pelvis to the inferior margin of the sternum and provides rigidity to the abdomen in lower animals, notably in sala-

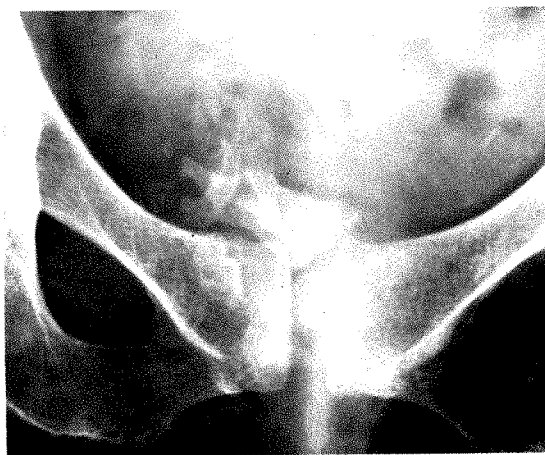


FIG. 8. Case VI. "Pseudo-marsupial bones" (myositis ossificans).

manders with functional lungs where it furnishes an attachment for respiratory muscles. Others are the epipubis, a spike-like cartilaginous structure projecting from the superior rim of the pubis in the cephalad direction, and, best known of all, the true marsupial bones for which the kangaroo is probably the most popular example. These are osseous structures which extend from the cartilaginous pubic symphysis in the cephalad direction pointing slightly ventrally. Their purpose has not been established with certainty but they seem to provide a mechanical support for the pouch and help the developing infants to suckle in that they exert counter pressure upon the mammary glands.

SUMMARY AND CONCLUSION

Five different types of symphyseal bridging have been described. Common to all is their noninfectious origin. Symphyseal bridging as a sequela to infection such as tuberculosis, typhoid fever, osteomyelitis and osteitis pubis has been excluded from consideration here. The cases presented fall into the following etiologic classes: degenerative, traumatic, surgical, rheumatic and myositic. The most common variety is the hook-shaped superior bridge seen in elderly patients. It is thought to represent essentially a degenerative type of lesion. The most unusual of the cases presented is the one that simulates the presence of marsupial bones.

New York Medical College
Center for Chronic Disease
Bird S. Coler Hospital
Welfare Island
New York, New York 10017

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A RE-EVALUATION OF THE "FISH VERTEBRA" SIGN IN SICKLE CELL HEMOGLOBINOPATHY*

By JACK REYNOLDS, M.D.

DALLAS, TEXAS

ALTHOUGH the fact was not recorded until 22 years after sickle cell anemia was first recognized as a pathologic entity, the disease affects the shape of the vertebral bodies in many of its victims.¹⁸ In some of these patients, a cup-like depression is formed in the upper and lower surfaces of the centrum, and the resultant contour is so distinctive that it is virtually pathognomonic of the hemoglobinopathy. However, proper emphasis has never been given to the diagnostic value of the unique structural features which serve to distinguish this lesion from the morphologically similar vertebral abnormalities caused by other diseases. And there is a lack of unanimity among observers concerning the way in which the pathologic mechanisms of sickle cell disease act to produce this deformity. It, therefore, seems appropriate to re-evaluate this manifestation of sickle cell hemoglobinopathy in the light of recent observations by discussing, in some detail, the manner in which the vertebral changes evolve and the characteristic shape of the deformity. In this way, the true nature of the typical roentgen signs may be established, and their diagnostic importance placed in proper perspective.

Described in geometric terms, the normal vertebral centrum is a right circular cylinder, the ends of which are formed by parallel flat surfaces which appear as straight lines when the spine is examined roentgenographically by the usual techniques. Minor variations in normal anatomic structure are not uncommon, particularly in the lower lumbar area, and pathologic deformities are encountered in a number of diseases. Such lesions are usually caused by the compression of weakened

bone which has been subjected to the stress of weight-bearing. Under such circumstances, the damaged bone usually assumes one of three basic shapes, as viewed roentgenographically: flat, wedge-shaped or biconcave. If the centrum is evenly compressed, it becomes flatter and wider than normal, yet retains its rectangular, straight-sided appearance. Eccentric collapse produces a wedge shape. The more complex, biconcave deformity is characterized by cup-like depressions which are produced in both the upper and lower surfaces of the vertebral body by the protrusion of the normal resilient, turgescient intervertebral soft tissue into the weight-bearing aspect of the weakened bone. In this form, the shape of the centrum resembles that found in certain lower vertebrates with larger notochordal remnants. In such species, the shape of the vertebral body conforms to the convex surface of the voluminous soft tissue which is interposed between the bony segments of the spine. Because of this similarity in bony contour, the term "fish vertebra deformity" has long been employed to describe this type of structural abnormality in humans (Fig. 1, *A*, *B* and *C*).

Several varieties of this metaphor exist. Its origin as a part of medical parlance is obscure, but it was probably introduced by a Boston radiologist who, influenced by provincial pisciculture and local dietary customs, used the species-specific phrase "codfish vertebra." The term "fish-bone deformity" has gained some currency, and the lesion is occasionally referred to as an "hour-glass deformity" by those who are "out of the swim of things." The original version is sometimes badly corrupted to "fish-tail vertebra," a term without appar-

* Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October 1, 1965.

From the Department of Radiology, University of Texas Southwestern Medical School, Dallas, Texas.

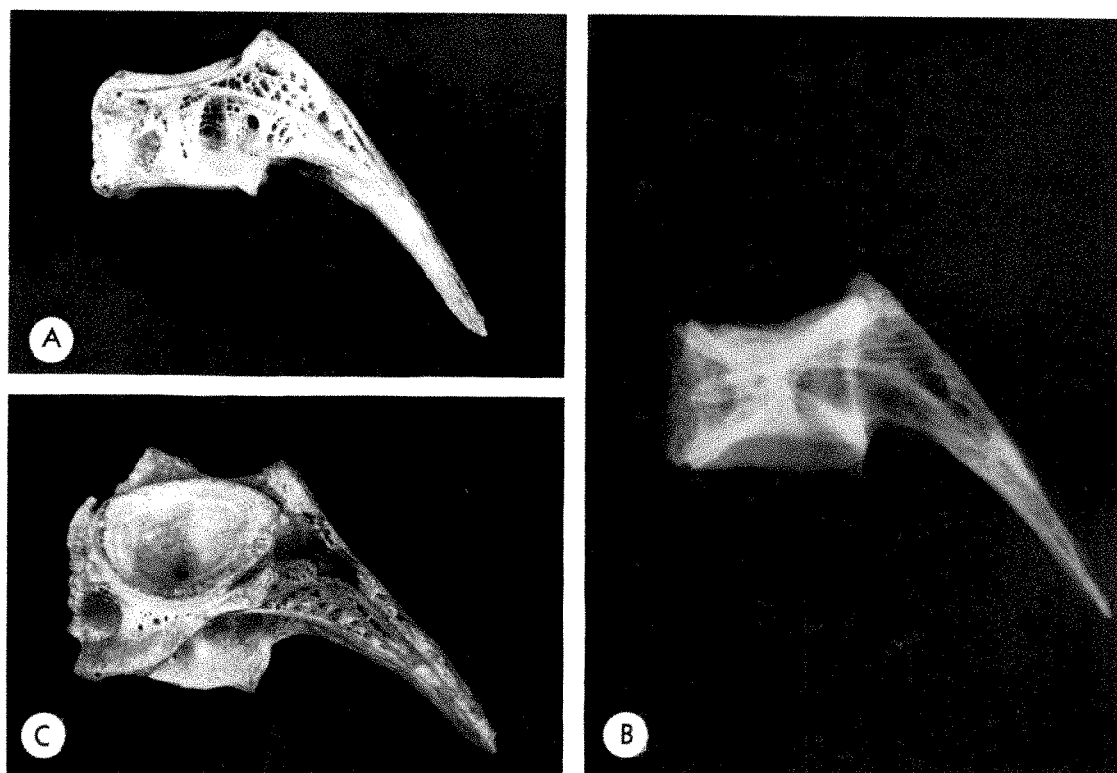


FIG. 1. A vertebra removed from the skeleton of a fish depicted (A) photographically and (B) roentgenographically. The conical shape of the cephalad surface of the centrum is shown in C. The roentgenogram, a lateral projection, demonstrates the biconcave contour of the vertebral body.

ent descriptive value. More credible is the analogy "fish-mouth deformity," a phrase which, although containing the word "fish," is apparently of different philologic origin since it was designed to describe, not the biconcave centrum, but the abnormal biconvex shape of the adjacent intervertebral disk.

The term was originally coined to describe the spinal changes which are most frequently observed in patients with senile osteoporosis or other diseases which produce dissolution of the rigid components of bone. As commonly employed, the appellation has come to imply the presence of an acquired lesion caused by the mechanical compression of bone which has become softened through the loss of its architectural integrity. The use of the term in this context was well established when, rather recently, it was first noted that cup-like depressions were present in the vertebral

bodies of some patients with sickle cell disease.^{13,16} And because the biconcave shape of the centra, as observed in the hemoglobinopathy, seemed to resemble the familiar fish vertebra deformity of osteoporosis, the same descriptive phrase was promptly applied, and quickly gained popular acceptance, when used to signify the cupping of the vertebral end-plates which is manifest in about 30 per cent of the adults with this blood dyscrasia.⁵

It has always been assumed that the basic pathologic mechanism responsible for this bony deformity in sickle cell disease is essentially the same as that which causes central collapse of the weight-bearing surfaces of the vertebral bodies in other, more common, diseases. This was a natural assumption since it was known that the rigid osseous tissue of the axial skeleton in sickle cell disease is subject to attrition through the damaging effects of infarction

and marrow hyperplasia which served to destroy trabeculae and weaken the bone.^{2,7,9,13,17} Indeed, while these pathologic processes are less destructive to bone than the osteolytic mechanisms of other diseases which effect the skeleton, they seem to play a major role in the production of the flat and wedge-shaped vertebral deformities which occur in those portions of the spine which are subjected to the greatest mechanical stress in patients with this hemoglobinopathy. But, if these assumptions are correct, and the fundamental mode of development and ultimate morphology of the biconcave deformity of sickle cell disease is no different from the fish vertebra deformity encountered in other disorders, then the detection of this lesion is of little value to the radiologist, for the sign would appear to lack specificity.

Fortunately for the diagnostician, however, there is evidence to suggest that these long accepted tenets are probably wrong.² More careful scrutiny of the morphologic characteristics of the so-called fish vertebra deformity as it occurs in sickle cell disease reveals certain features which serve to set it apart from the simple biconcave shape seen in these other disorders. Its unique structural qualities not only provide the radiologist with a highly specific and, therefore, valuable sign, but they also suggest that this vertebral deformity in sickle cell disease develops as a direct result of complex pathologic mechanisms which are peculiar to the hemoglobinopathy. And the evidence indicates that, unlike the classic "fish vertebra deformity," this form of end-plate distortion is actually a developmental defect and not an acquired lesion (Fig. 2).

The features which characterize this lesion and set it apart are best described in terms of the way it differs from the more familiar deformity commonly encountered in patients with osteoporosis (Fig. 3, *A* and *B*; and 4, *A* and *B*). In all such disorders, in which dissolution of the rigid supporting elements of bone permits cup-like distortion of the weight-bearing aspects of the vertebral bodies, the entire surface of the



FIG. 2. A portion of the thoracic spine of a young adult with sickle cell hemoglobinopathy in lateral projection. Near the center of each "end-plate," the normal plane surface is deformed by a well defined, cup-like depression. Characteristically, both surfaces of each centrum exhibit identical depressions, and the shape of all of the involved segments is strikingly uniform. These structural features, which serve to distinguish this lesion from vertebral deformities of other etiologies, are ideally portrayed in this patient. (Reproduced with permission.²¹)

end-plate is altered so that a rounded depression is formed which extends in a smooth, continuous curve from the depth of the central indentation, all the way to the periphery of the vertebral body. The contour thus formed has no plane surfaces; therefore it is truly concave. In the deformity produced by sickle cell disease, however, the typical depression in the end of the centrum is different both in size and shape. Characteristically, the defect does *not* involve all of the end-plate and, therefore, it does not form a smooth concavity across the entire surface. Instead, the cup-like depression is confined to the central

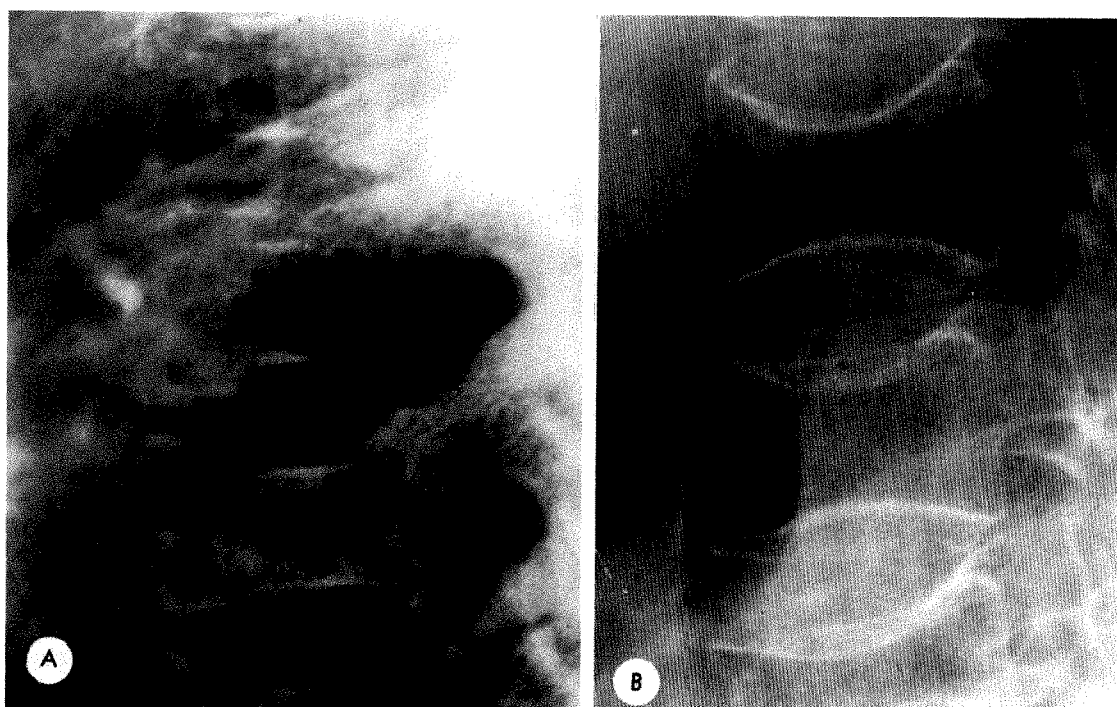


FIG 3. (A) Lateral view of the vertebral centra of a young patient with the SS genotype showing the pattern of deformity which is typical of sickle cell disease. (B) The centra of an elderly subject showing the classic biconcave contour of the sort commonly caused by osteoporosis for which the term "fish vertebra deformity" was originally coined. This illustration permits easy comparison of the two entities, and it is evident that, although both are characterized by "end-plate" deformities, they are actually quite dissimilar (see Fig. 4, A and B).

zone so that the periphery retains its normal flat surface. As a result, the centrum does not lose its "squared" or rectangular appearance. The deformity is also unique in that the "floor" of the central depression, instead of being rounded, is formed by a flat plate of dense bone.

These peculiarities in the topography of the end-plate are of the greatest importance, but there are other features which also serve to indicate the fundamental differences which exist between this vertebral lesion of sickle cell disease and the biconcave deformity produced by other disorders. In the hemoglobinopathy, the depressions in the upper and lower surfaces of the centrum are almost identical in shape and depth, whereas this symmetry is commonly absent in the deformity produced by the simple collapse of weakened bone. In senile osteoporosis, for example, one end-

plate is usually more deeply depressed than the other. Similarly, the manner in which this lesion is distributed through the spinal column in senile osteoporosis lacks the uniformity which characterizes the pattern seen in sickle cell disease. When the deformity is present in patients with the hemoglobinopathy, it often extends throughout most of the spinal column to involve a number of contiguous segments. And, typically, the shape of each of the deformed centra is remarkably alike. In senile osteoporosis, however, it is rare for two deformed segments to appear identical, and vertebrae with normal contours are frequently seen interposed between groups of collapsed vertebrae.²⁰

It is also interesting to note that the depth of the concavity in the surface of the centra in sickle cell disease is unrelated to the magnitude of mechanical stress pro-

duced by the upright posture. Unlike the pattern produced by weight-bearing on weakened bone, in which the greatest compression and deepest concavities occur in the lower spine, the biconcave deformity is often most clearly defined in the thoracic region in patients with hemoglobinopathy. And not uncommonly, prominent cupping extends upward into the cervical segments, despite the fact that they are subjected to only slight compression from the weight of the head (Fig. 5, *A* and *B*).

In attempting to form an hypothesis to explain the manner in which cupping of the centra is produced in sickle cell disease, it must be considered that either or both of the pathologic mechanisms at work in the

hemoglobinopathy may act to adversely affect the structural integrity of bone and thus play a role in shaping the lesion. In compensation for severe, chronic hemolytic anemia, the rate of erythropoiesis is accelerated. The resultant marrow hyperplasia is particularly exuberant in the axial skeleton where the medullary bone of the centra takes on a dark red, jelly-like consistency, and the cancellous spaces become enlarged.⁷ This overgrowth of the soft, cellular components of bone has some effect on the ability of the centra to withstand mechanical stress, but it seems unlikely that it plays the primary role in producing the biconcave deformity. As Henkin¹³ pointed out, if marrow hyperplasia alone were capable of

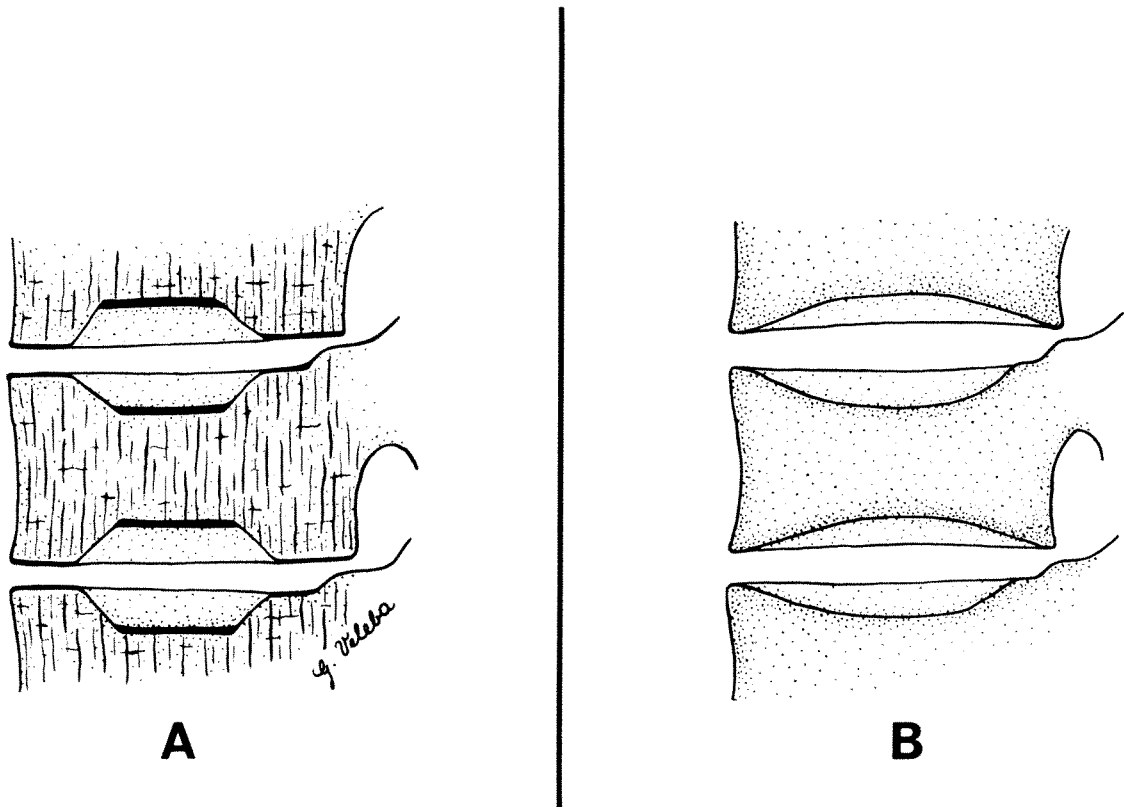


FIG. 4. The morphologic differences between the cup-like defect typical of sickle cell disease and the truly concave deformity produced by the compression of osteoporotic bone are illustrated diagrammatically. (*A*) The lesion of sickle cell disease. Note that only the central portion of the "end-plate" is depressed and that the "floor" of the depression is formed by a flat plate of thickened bone. (*B*) The biconcave deformity caused by the collapse of soft bone. Note that the entire surface of the "end-plate" is altered to form a continuous curve across the width of the centrum. The depression is smoothly rounded; no flat surfaces remain. (Reproduced with permission.²¹)

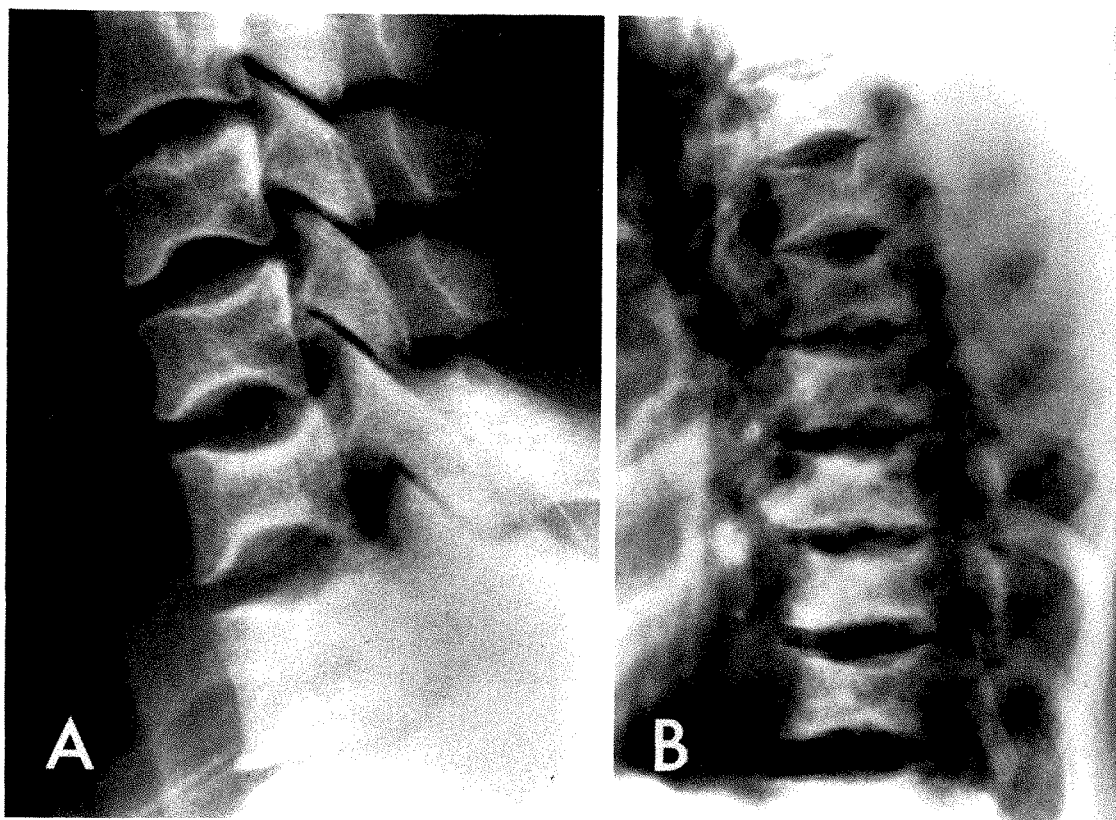


FIG. 5. Two views of the spine of a middle-aged male with sickle cell disease in lateral projection. (A) The middle and lower portions of the cervical spine. (B) The middle and lower portions of the thoracic spine. The cup-like vertebral deformity, typical of the hemoglobinopathy, is seen in both regions. The sclerotic appearance of the lower thoracic centra is caused by the repair of bone infarcts. Note that the concave depressions in the more cephalad segments of the spinal column appear larger and deeper than those in the lower thoracic region where the greatest weight is borne. This pattern of distribution would seem to indicate that simple mechanical stress does not play a major role in the production of this type of vertebral deformity in sickle cell disease.

weakening bone enough to permit the formation of surface depressions, then this vertebral deformity should occur with great regularity in patients with thalassemia major, a form of anemia in which compensatory overgrowth of red marrow is even more profuse than it is in sickle cell disease. But such is not the case (Fig. 6). Vertebral collapse is not a feature of the other hemolytic anemias, nor is there a positive correlation between the severity of the anemia and the magnitude of the vertebral deformity among patients with the various symptomatic forms of sickle cell hemoglobinopathy. Patients with sickle cell-hemoglobin C disease, in whom the

degree of anemia is relatively mild, often exhibit vertebral cupping in its most extreme form. And it is noteworthy that many victims of the "milder" forms of sickle cell hemoglobinopathy, instead of enjoying a degree of protection from the damaging effects of intravascular sickling and its sequelae, actually suffer severe morbidity from this process. Thus, it seems likely that circulatory stasis and ischemia is the pathologic mechanism which is primarily responsible for the development of the distinctive vertebral lesion in sickle cell anemia.

Although the changes produced in the spine by local tissue ischemia undoubtedly

cause the dissolution of trabeculae and thus would seem to favor collapse of the sort commonly seen in osteoporosis, evaluation of the evidence at hand suggests that the classic vertebral deformity of sickle cell disease is not acquired by the destruction of existing bone. Instead, it is proposed that the lesion is actually a developmental aberration caused by the noxious effects of chronic ischemia which act to retard endochondral bone formation. The lesion is best viewed as a defect in the growth and development of bone which evolves as a direct manifestation of the fundamental pathologic mechanism which characterizes this disease of the erythron.

Insight into the nature of the pathogenesis of this vertebral lesion is provided by the knowledge which has been gained concerning the effects of infarction on growing bone in other parts of the skeleton. It has long been known that interruption of the metaphyseal blood supply in the region immediately adjacent to the growth plate of a long bone retards the elaboration of new bone. If circulation throughout the metaphysis is impaired, longitudinal growth ceases in the affected bone. If, however, a focal lesion is produced which involves only a portion of this vital area, then the effects of ischemia on growth are limited to the site of injury, and growth progresses normally elsewhere in the growth zone. As a result, the contour of the growth plate becomes altered, and changes are produced in the shape of the metaphysis and epiphysis of the developing structure.^{6,14}

Skeletal distortion of this sort, caused by the effects of mechanical trauma or radiation on the metaphyseal circulation of growing bone, has been studied by a number of observers,^{1,12,24} but it was Cockshott⁶ who first drew attention to the spontaneous development of osseous growth deformities in patients with sickle cell disease following vascular occlusion. In young patients with this hemoglobinopathy, marrow hyperplasia takes place, not only in the axial skeleton, but in the extremities as well. The

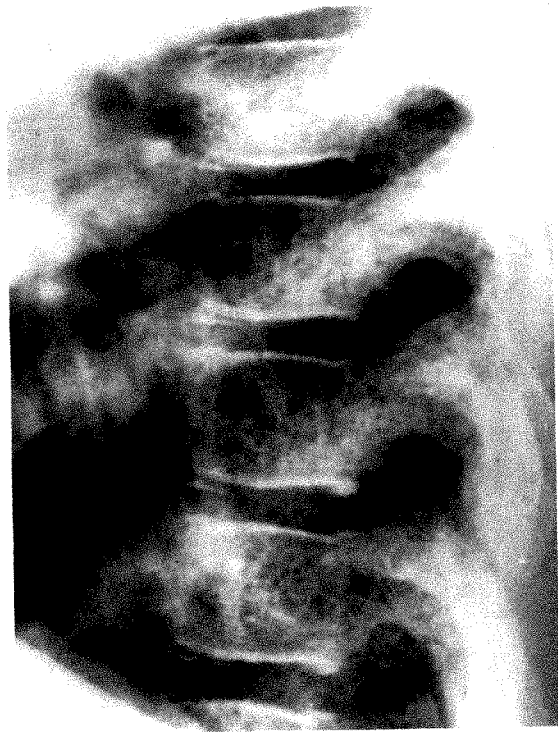


Fig. 6. The lower thoracic spine of a 15 year old patient with thalassemia major. Note that the vertebral centra show no deformity despite the presence of extreme marrow hyperplasia which characterizes this disease. Apparently, the overgrowth of the soft erythropoietic tissue, alone, does not weaken bone enough to cause compression and distortion of the weight-bearing surfaces. (Reproduced with permission.²¹)

presence of hyperplastic marrow in the appendicular skeleton seems to provide a physicochemical milieu which favors the sickling of red blood cells as they circulate through these bones. Due to regional circulatory stasis produced in this manner, these children sometimes suffer painful infarction of the tubular bones of the hands and feet resulting in the so-called "hand-foot syndrome"²⁵ (Fig. 7). Following such an episode, most of the damaged bone is quickly repaired. But occasionally, the central portion of the growth plate is permanently deranged, and although longitudinal growth again proceeds at the periphery of this zone, it is retarded centrally. Thus, in time, the metaphysis assumes a cup-like shape. The floor of this depression is formed

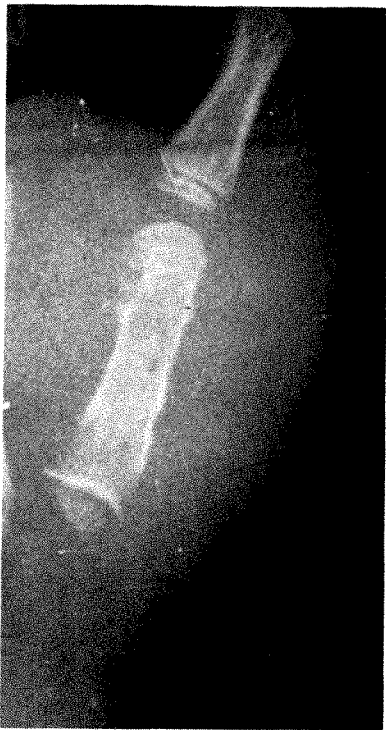


FIG. 7. The first metacarpal of a young child with sickle cell disease showing the extensive diaphyseal damage caused by massive infarction. The study was performed about 4 weeks after the onset of pain and swelling.

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by a flat plaque of compact bone which appears as a dense linear shadow on the roentgenogram, marking the site occupied by the damaged growth plate at the time of the acute episode (Fig. 8, *A* and *B*).

The metaphyseal deformity assumes this characteristic shape because only a portion of the growth plate is subjected to ischemic damage and growth arrest, and this occurs in the "hand-foot syndrome" as a direct result of the vascular anatomy and circulatory dynamics of the metaphysis (Fig. 9). The metaphysis receives arterial blood from two sources, each of which perfuses a different part of this zone, and only one of which is

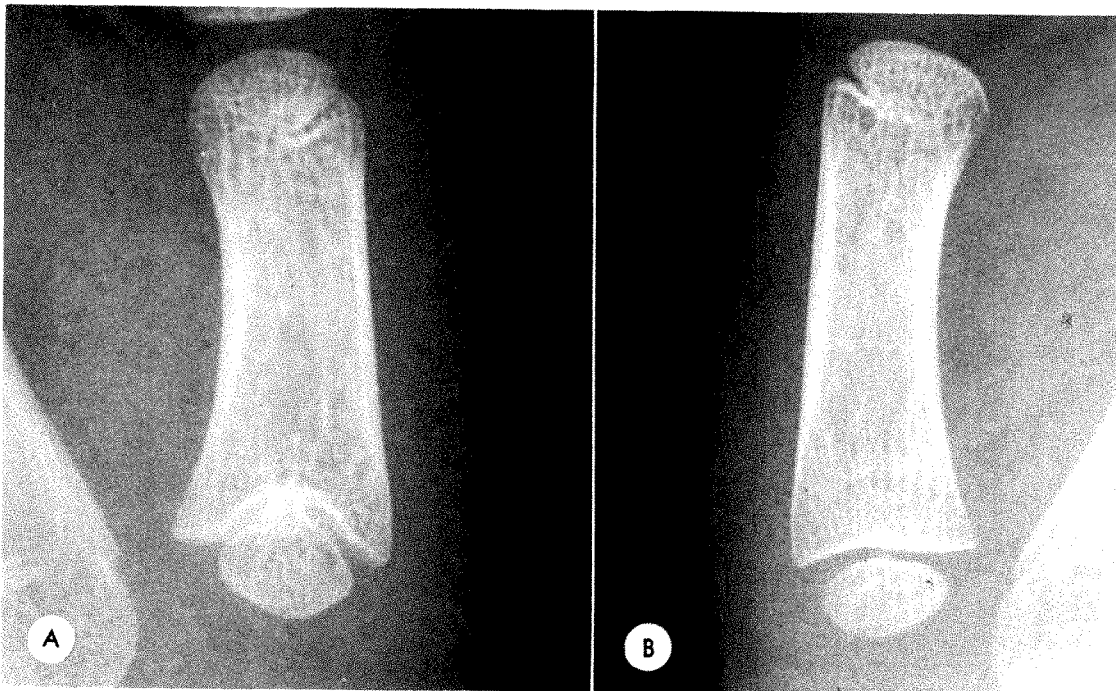


FIG. 8. (*A* and *B*) The first metacarpals of a 5 year old boy with sickle cell disease. Note the deformity of the metaphysis and epiphysis in *A*. This was caused by an earlier diaphyseal infarct which occluded the vessels supplying the central portion of the growth plate. As a result of ischemic injury, growth was arrested in this zone, but progressed normally at the periphery. The metaphyseal cup-like deformity which was produced in this manner resembles the central depression which characterizes the "end-plate" deformity seen in the vertebrae of older patients with this disease.

compromised by the diaphyseal infarction (Fig. 10). The outer margin of the metaphysis does not become ischemic because it receives its arterial supply, through short perforating vessels, directly from the periosteal circulation, and these remain patent. The central portion of the metaphysis, however, is dependent upon branches of the nutrient artery which must course through the congested, devitalized diaphyseal marrow where increased intramedullary pressure and intravascular sickling produce vascular occlusion and circulatory stasis.^{14,23,24}

Attention is now directed to the way in which the shape of the deformed metaphyses in the tubular bones of the extremities, where the distortion is known to be due to the effects of ischemia on bone growth, resembles the contour of the deformity seen in the upper and lower sur-

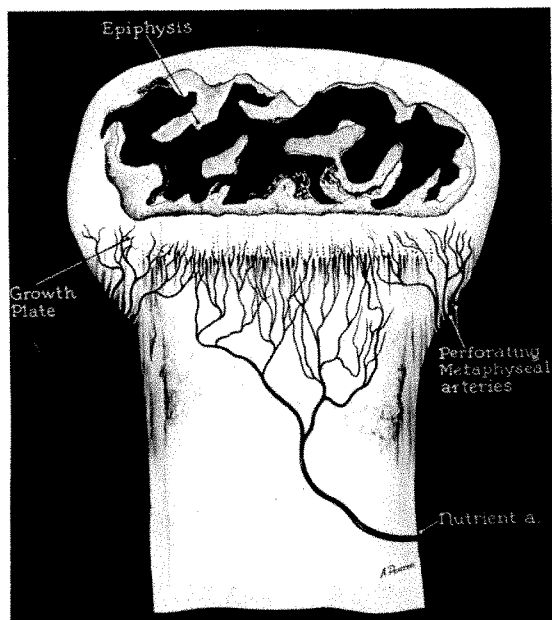


FIG. 9. A schematic drawing designed to illustrate the metaphyseal region of a metacarpal and the sources of its blood supply. Note that the area adjacent to the periphery of this growth plate receives arterial blood directly through short perforating vessels derived from the periosteal circulation, whereas the central portion of the metaphysis is dependent upon branches of the nutrient artery which must course for some distance through the diaphysis.

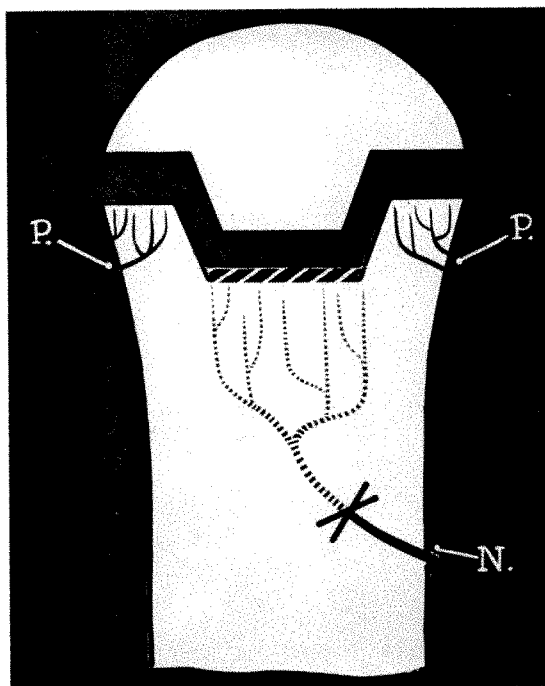


FIG. 10. Simplified diagram showing the characteristic shape of the cup-like metaphyseal deformity which develops in the metacarpal following diaphyseal infarction. As indicated here, the nutrient artery (N.), which normally supplies the central metaphyseal area, becomes occluded at the time of the acute episode. The resultant central ischemia causes growth arrest in this zone, but the periphery of the metaphysis, being supplied by perforating arteries from the adjacent periosteum (P.) which are not occluded by diaphyseal congestion, is not subjected to ischemia, and normal growth occurs in this area. The flat, thickened "floor" of the depression marks the site occupied by the central zone of the growth plate at the time of the infarct.

faces of the centrum in sickle cell disease. Both lesions are characterized by a central, cup-like depression, the floor of which appears to be formed by a small flat plate of compact bone.

It is often unwise to assume that because two lesions look alike they may both have been produced by the same pathologic mechanism. But, in this case, the assumption gains support from the fact that the site in which the lesion develops in each of these bones shares a common toponymy and function. And perhaps most important, the anatomic distribution of the arteries

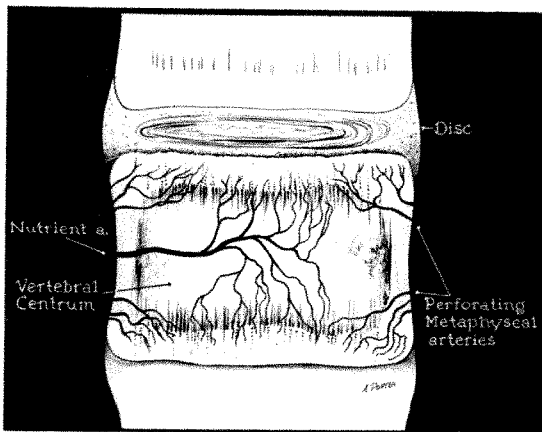


FIG. 11. A schematic drawing of a vertebral centrum designed to illustrate the origin and distribution of the arteries which supply the layers of bone immediately adjacent to the cephalad and caudad surfaces. During maturation, endochondral bone formation takes place in these zones to produce vertical growth of the centrum. The zones are, therefore, analogous to the metaphyses of the long bones (see Fig. 9). Note that the anatomy of the circulation in the vertebral metaphyses and in the metaphysis of the metacarpal is the same. In both bones, the central portion of the growth plate is dependent upon branches of the nutrient artery, while the periphery is not.

supplying this portion of the vertebral centrum conforms to the same pattern seen in the metaphyses of the tubular bones of the extremities. The cephalad and caudad aspects of the vertebral body are, in fact, the metaphyses of this bone. Plates of cartilage overlie these plane surfaces, and vertical growth of the centrum is brought about through the process of endochondral bone formation in these sites.^{3,10,11,15} As in the metaphyseal region of the long bones, the periphery of these plate-like growth zones receives its blood supply directly, via short, perforating branches of the periosteal arteries, while the central portion of the metaphysis is dependent upon branches of the nutrient artery which, upon entering the centrum at a remote point, must traverse the marrow to reach this vital area⁸ (Fig. 11). It seems evident then, that just as in the metacarpal, any pathologic process affecting the medullary bone of the vertebral body might easily impede circula-

tion to the central metaphyseal region without interfering with the flow of blood to the periphery of the growth plate. Thus, the anatomic structure and circulatory dynamics of the metaphyses of the vertebral centrum make it possible for the surfaces to become deformed through the effects of local ischemia on bone growth (Fig. 12). And it would appear that vertebral cupping, as manifest in sickle cell disease is, indeed, induced in this manner.

However, the way in which this mechanism is initiated within the centrum is still a matter of conjecture; the precise nature of the physical forces which alter the vertebral marrow to impede circulation through the branches of the nutrient artery remains to be explained. Unlike the development of this deformity in the metacarpals, which is preceded by overt evidence of acute dia-

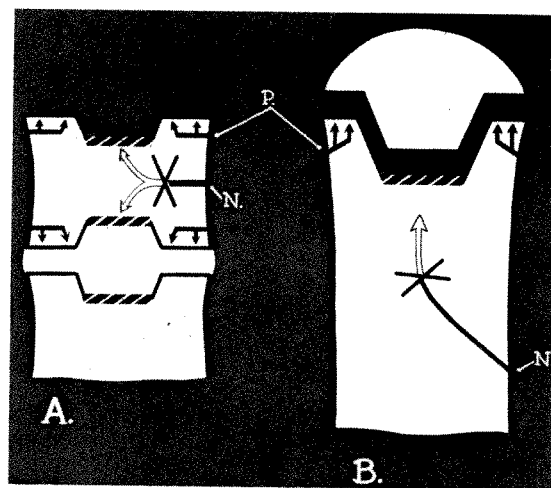


FIG. 12. A simplified diagram which permits comparison to be made between the shape of the defect produced by sickle cell disease in the metaphyses of the vertebral centrum (A.) and in the metaphysis of the metacarpal (B.). Note that, in both, the cup-like deformity is centrally placed, and that the "floor" of the depression is formed by a plate of thickened bone. The diagram also shows that the anatomic distribution of the arteries supplying the metaphyses is the same in both bones, and that conditions which impede circulation through the nutrient artery (N.) to produce metaphyseal ischemia and growth arrest fail to affect the periphery of the growth plate which is perfused by a separate arterial source (P.).

physeal infarction which inevitably produces stasis in the medullary circulation, the pathologic mechanisms which must act in the vertebral marrow to cause vascular blockade are more subtle. Clinical observations provide few clues to suggest the pathogenesis. Although most patients with sickle cell disease who have developed distinctive vertebral cupping report having suffered repeated "crises" during which back pain was present, frequent painful attacks of the same sort are also experienced by patients who show no vertebral changes. And strangely, extensive end-plate deformity is sometimes observed in individuals who recall no episodes of skeletal pain.^{17,22} While acute, massive ischemic necrosis of the vertebrae has been reported, this is very rare in sickle cell disease.^{9,17} It seems likely that, in the spine, local ischemia and the resultant deformities are produced either by the cumulative effects of repeated small episodes of intramedullary infarction (which may correspond to the bouts of back pain), or by the insidious effects of local low-grade, chronic anoxia which, while severe enough to interfere with bone growth, might allow existing tissue to survive. Both of these processes may act concomitantly to play causative roles. The voluminous, hyperplastic red marrow which is present throughout the spine, even in patients with the mixed forms of this hemoglobinopathy, would seem to provide conditions which are conducive to metaphyseal anoxia, not only by altering local metabolic demands, but by physically retarding free blood flow to prolong the circulation time. These conditions favor the reduction of oxyhemoglobin to its more insoluble state, and sickling then occurs at an accelerated rate which further increases hemic viscosity. The oxygen tension in tissue served by the terminal branches of an artery perfusing a region of this sort might well be critically reduced. Thus, circulatory stasis might easily occur which, if prolonged, could cause focal necrosis and permanent tissue damage.

There is further evidence, based on the

manner in which the skeletal changes evolve, to support the thesis that this distinctive deformity of sickle cell disease is due to a defect in bone development and is not acquired through the collapse of weakened bone. Marrow hyperplasia and infarction, pathologic processes which might be expected to affect the structural integrity of the centrum and thus permit it to become compressed and deformed by weight-bearing, begin to produce changes in the vertebral spongiosa during the first year of life, and continue inexorably. If the replacement of existing osseous tissue by these mechanisms were the primary cause of the biconcave deformity, one would expect to see vertebral distortion begin in early childhood and become progressively more severe with passage of the years. But this does not occur. Instead, during the first decade of life when growth is progressing at a moderate rate, the centra retain their normal contour. Although distortion of the "end-plates" has been reported in patients 7 years old, it is rarely observed before the age of 10 years.¹⁹ The onset seems to be delayed until the centra reach a critical size. Perhaps, in the small vertebral metaphyses of the young child, some protection against central ischemia is provided by collateral vessels derived from the periosteal arteries of the periphery, but, as the diameter of the growth plate increases, its central portion becomes more vulnerable.¹⁴ In patients destined to develop vertebral cupping, signs of this stigma usually begin to appear near the advent of adolescence. Then during the ensuing 6 or 8 years in which bodily stature increases at an accelerated rate, the shape of the centra changes rather rapidly. And before the end of the second decade of life, when physical maturation ceases, the evolution of the vertebral deformity reaches its end-stage. Thus, the mechanism which produces this unique spinal lesion in sickle cell disease achieves its ultimate result before the patient enters adulthood (Fig. 13, *A* and *B*). And, although the morbid processes which characterize the hemoglobinopathy continue un-

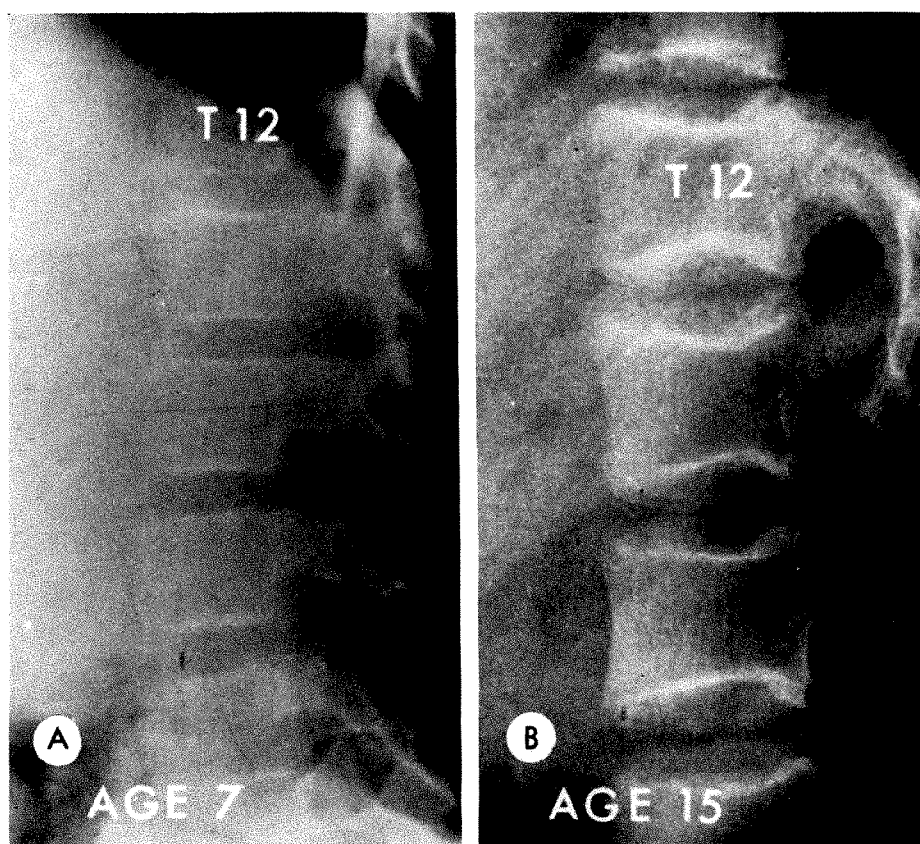


FIG. 13. (*A* and *B*) Two roentgenograms of the spine of a young female with sickle cell disease, taken 8 years apart, which illustrate the manner in which the biconcave deformity of the centra evolves. Note that, despite having been subjected to the stress of weight-bearing since early childhood, the centra are normal in shape at the age of 7 years. As if influenced by the period of rapid growth which accompanies adolescence, however, the characteristic cup-like deformity has become clearly manifest by the age of 15 years.

abated, the basic shape of the distorted bone remains "set" (Fig. 14, *A* and *B*).

From these observations, it seems evident that the pathogenesis of the lesion is a phenomenon related to the bodily changes which accompany adolescence. Its entire course of development is correlated in time with the period of most rapid growth, and these changes cease once skeletal maturation is at an end. The circumstances which exist during the time of its evolution, therefore, are exactly those which would be expected to accompany the development of a defect produced by an aberration of bony growth.⁴

In some patients the distinctive morphologic features of the lesion undergo minor

modification; the "squared-off" shape of the deformed end-plates may lose its distinct rectangular quality as the normal flat surface at the periphery of the vertebral body is later distorted to become smoothly confluent with the curved sides of the central depression. If this happens, the cup-like deformity appears to enlarge laterally to involve more of the surface, and its contour, becoming more curvilinear, tends to conform to the truly concave shape which characterizes the common type of fish vertebra deformity caused by compression of weakened bone. However, secondary changes of this sort serve only to modify the unique features of the lesion. They fail to obscure the signs which mark the site of

growth arrest. And despite these minor alterations in the original contour, the straight, thickened layer of compact bone which forms the flat floor of the cup-like depression at the center of the "end-plate" remains to indicate the fundamental nature of the developmental aberration. This sign, therefore, serves the radiologist with a reliable means of distinguishing the vertebral growth deformity of sickle cell disease from the biconcave deformity, which occurs in other disorders.

Despite the fact that the cup-like vertebral deformity of sickle cell disease is a unique manifestation of this disease and

differs, both in its form and pathogenesis, from the common spinal abnormality for which the phrase "fish vertebra deformity" was devised, this descriptive term is freely used in medical communications to designate the spinal changes which characterize the hemoglobinopathy. This is unfortunate because the phrase, having come to connote the destruction and collapse of bone, spuriously implies the existence of features which are not present in the lesion of sickle cell disease. However, it must be conceded that, while the two types of deformities differ, the shape of each bears some resemblance to the vertebra of a fish, and, as yet,

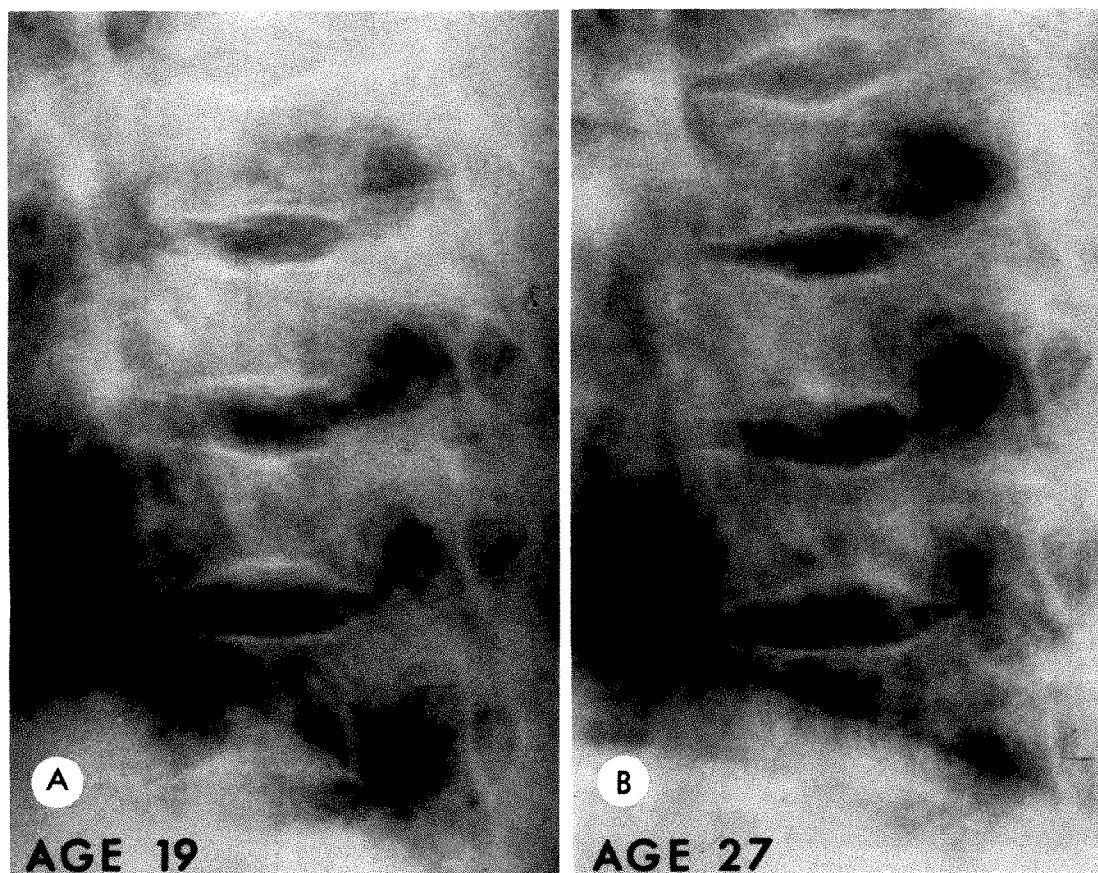


FIG. 14. (A and B) Two roentgenograms of the lower thoracic spine of a male with sickle cell disease, taken 8 years apart, showing that the shape of the deformed centra remains relatively constant once skeletal maturation has been achieved. At the age of 19 years, when vertical growth of the vertebral bodies was virtually complete, the cup-like defects had already assumed their final form. Later, at the age of 27 years, despite continued symptomatic disease and the force constantly exerted by the upright posture, the surface depressions are no deeper than they were at the end of adolescence when the vertebral growth plates ceased to produce new bone.

no substitute form of descriptive imagery has been fashioned to succinctly indicate the unique qualities of this stigma of the hemoglobinopathy. Nevertheless, the popular use of the term "fish vertebra deformity" to describe this lesion as it is manifest in sickle cell disease is ill-advised, for it helps to foster a false concept.

SUMMARY

The so-called fish vertebra deformity as manifest in sickle cell disease is shown to be different, both in contour and mode of development, from the familiar type of biconcave deformity commonly seen in the osteoporotic spine. The distinctive structural features which characterize this lesion are described. The deformity is unique in its local topography, its uniformity, and the manner in which it evolves.

Evidence based on a consideration of the contour of the defect and its location within the bone indicates that it is produced, not by the destruction and compression of existing bone like the common types of fish vertebra deformity, but by the local inhibition of bone growth as the result of regional ischemia. The "end-plates" of the growing centra where cupping takes place are functionally analogous to metaphyses, and the regional vascular anatomy is such that only the central portion of the growth plate suffers ischemic damage when circulation is impaired through the branches of the nutrient artery. These features control the shape of the deformity. The period during which the deformity evolves is closely correlated in time with the age of rapid growth, and this also marks the lesion as an aberration of bony development.

Although the "fish vertebra deformity" of sickle cell disease, as viewed roentgenographically, exhibits structural characteristics which can serve to distinguish it from the similar but not identical vertebral lesions produced by other disease entities, the diagnostic information provided by these unique morphologic features has never been properly exploited by the radiologist, despite the fact that the distinctive signs are

virtually pathognomonic of the hemoglobinopathy.

Department of Radiology
University of Texas Southwestern Medical School
Dallas, Texas

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NEW BONE PRODUCTION AND PERIOSTEAL REACTION*

By JACK EDEIKEN, M.D., PHILIP J. HODES, M.D.,
and LAWRENCE H. CAPLAN, M.D.
PHILADELPHIA, PENNSYLVANIA

NEW bone production, a frequent finding in many bone conditions, may originate from normal bone forming elements (trabeculae and periosteum) or from tumor cells. Whereas osteogenic and chondrogenic tumors alone are able to produce tumor new bone, many neoplasms, as well as infection, trauma and other disease, can stimulate reactive new bone. It is of para-

mount importance to differentiate the one from the other.

When *new bone* forms within a host bone, it may be difficult to differentiate *tumor new bone* from *reactive new bone*. *Reactive new bone* usually is represented by thickening and increased density of pre-existing trabeculae. It is orderly and organized. *Tumor new bone* within a host bone may appear as a nest or nests of ivory-like density (Fig. 1) or as multiple dense flecks of bone (Fig. 2). The former are produced by osteogenic tissue (osteosarcoma and osteoblastoma); the latter are produced by chondrogenic tissue (chondrosarcoma, chondroblastoma, and chondroma). As no tumors other than chondrogenic or osteogenic produce *tumor new bone*, once it is identified the differential possibilities are considerably narrowed.

When new bone forms at the periphery of a host bone, it may be due to tumor new bone or periosteal reaction. Periosteal

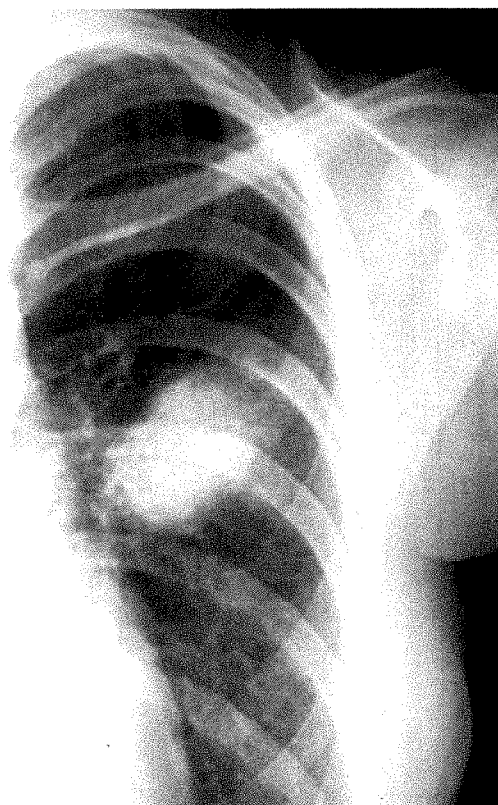


FIG. 1. Tumor new bone due to osteosarcoma. New bone formation is seen within the anterior portion of the third rib due to osteosarcoma. The dense homogeneous density is characteristic of new bone formation of osteogenic tumor.



FIG. 2. Tumor new bone formation due to chondrosarcoma. The large mass extending from the ramus of the pubis contains multiple flecks of calcification. This type of calcification is characteristic of cartilaginous calcification and indicates the presence of a chondrogenic tumor.

* From the Department of Radiology, Jefferson Medical College Hospital, Philadelphia, Pennsylvania.

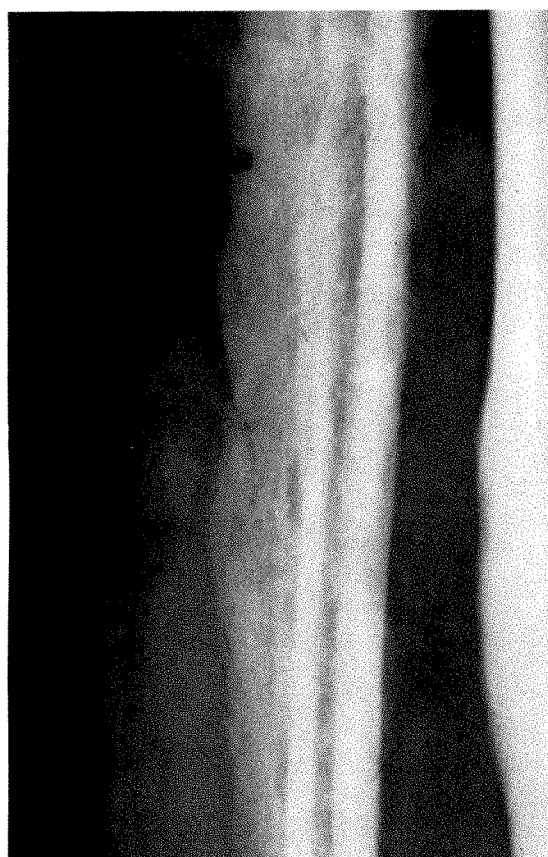


FIG. 3. Dense undulating periosteal reaction secondary to longstanding peripheral vascular disease. There is periosteal new bone formation most noticeable on the lateral aspect of the fibula. The external surface is undulated. The periosteal reaction is quite thick and almost homogeneous and indicates a benign process.

tumor new bone has the same characteristics as tumor new bone within the host bone. It is produced by soft tissue extensions of primary bone tumors.

Periosteal reactions are common occurrences in bone lesions. Despite their ease of recognition roentgenographically, there exists considerable misapprehension regarding their significance.

Periosteal reactions may be described roentgenographically as (1) solid or (2) interrupted (Table 1).

I. SOLID PERIOSTEAL REACTIONS

The *solid periosteal reactions* may be defined as a single layer of new bone greater

TABLE I

Type	Example
<i>I. Solid Periosteal Reaction</i>	
A. Thin	Eosinophilic Granuloma and Osteoid Osteoma
B. Dense Undulating	Vascular
C. Thin Undulating	Pulmonary Osteoarthritis
D. Dense Elliptic	Osteoid Osteoma
1. With Destruction	Long-Standing Malignant Tumors
E. Cloaking	Storage Diseases, Chronic Infection
F. Codman's Triangle	Hemorrhage and Malignancy
<i>II. Interrupted Periosteal Reaction</i>	
A. Lamellated (Onion Peel)	Osteosarcoma, Ewing's Tumor and Infection
B. Perpendicular (Sunburst)	Osteosarcoma, Ewing's Tumor and Infection
C. Amorphous	Malignant Tumor



FIG. 4. Solid undulating periosteal reaction due to longstanding varicosities. Periosteal reaction is most noticeable on the fibula in the anteroposterior projection. The external surface is undulating and the reaction is solid. Notice the soft tissue changes due to longstanding varicosities.

than 1 mm. in thickness. They are of uniform density; the entire sheet of periosteal new bone looks the same. Remarkable differences may be seen from patient to patient, but in the individual patient, the newly formed bone, deposited as the result of periosteal reaction to an irritant, has an even, uniform, solid appearance. When seen, it is the hallmark of a benign process.

Essential in the recognition of solid periosteal reactions is its persistence, relatively unchanged for weeks. Whereas it may increase in size, the uniformity of its roentgen density changes but little. In this regard the importance of roentgen techniques cannot be overemphasized. One should be able to reproduce roentgenograms of uniform quality in order that reliable roentgen compari-

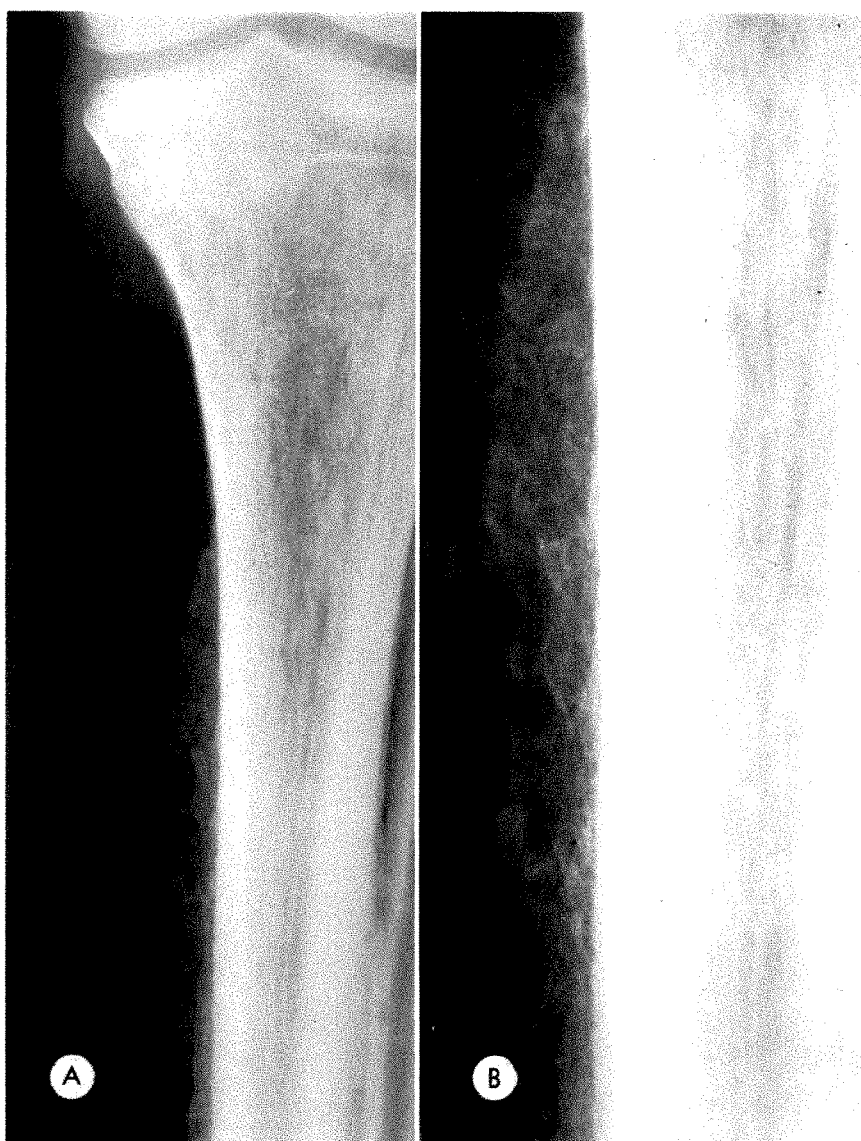


FIG. 5. Dense undulating periosteal reaction due to pulmonary osteoarthropathy. The periosteal reaction is quite thick. Initially, a small dense periosteal reaction may be noted but as the condition progresses it becomes much thicker and irregularly calcified. (A) Standard roentgenogram. (B) Magnified roentgenogram.



FIG. 6. Solid thin periosteal reaction due to pulmonary osteoarthropathy. Most of the metacarpals and phalanges reveal periosteal proliferation. This occurs relatively early and the appearance is solid.

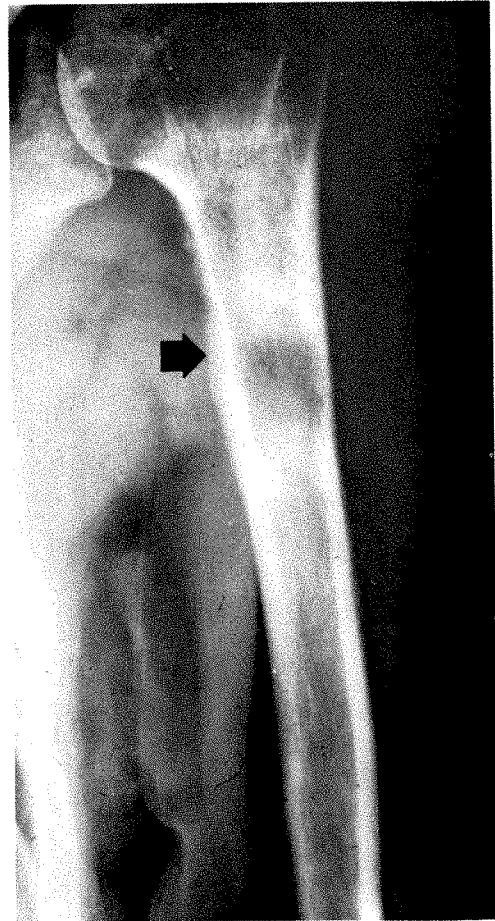


FIG. 8. Solid periosteal reaction secondary to osteomyelitis. This lesion was asymptomatic and discovered on a routine chest roentgenogram. The solid periosteal reaction on the medial aspect of the humerus at the site of the osteolytic destruction indicated the benign nature.



FIG. 7. Dense elliptic periosteal reaction due to long standing osteoid osteoma. The solid nature of the reaction indicates benignancy.



FIG. 9. Solid periosteal reaction due to osteoid osteoma. The solid nature of the periosteal reaction suggests benignancy.

sons may be made in successive follow-up roentgenograms.

Solid periosteal reactions vary from patient to patient depending upon the nature and course of the patient's illness. As an example, in one individual eosinophilic granuloma may produce minor periosteal reaction with but a thin layer of periosteal new bone. In a second, the reaction may be more aggressive with a thicker periosteal response. Yet, in both patients the periosteal new bone appears solid and uniform. They may differ remarkably in density as well as thickness. It is their uniformity and solidarity that are important, not their thickness or density. The latter only signify the progress and age of periosteal response.

Morphologically, solid uniform periosteal new bone may be thick or thin, of any degree of density, and have an even or undu-

lating superficial surface. Thickness and density seem related to the aggressiveness of the irritant. Duration, too, may play a part. Thus, low level irritants acting for longer periods of time or more aggressive irritants acting for shorter periods of time may eventuate similar roentgen changes. Regardless of time and intensity, the periosteal response in benign conditions usually will be even and uniform.

Among the lesions that commonly produce solid periosteal new bone may be included eosinophilic granuloma, fractures, osteomyelitis, hemorrhage, hypertrophic pulmonary osteoarthropathy, osteoid osteoma, vascular diseases, and the storage diseases.

Noteworthy is the fact that, whereas



FIG. 10. Solid periosteal reaction due to eosinophilic granuloma. The large destructive area in the humerus associated with periosteal reaction was considered Ewing's sarcoma. The solid nature of the periosteal reaction should suggest a benign condition.

solid uniform periosteal reactions bespeak benignancy, it must be remembered that benign lesions may not always express themselves in this classic manner. They may cause periosteal responses highly suggestive of malignant disease.

Dense undulating periosteal reactions often occur with longstanding varicosities or arterial disease. The periosteal reaction often is 1 cm. or more in thickness, and its free edge is rough and undulating (Fig. 3; 4; and 5, *A* and *B*). The mechanism of production is unknown.

Thin undulating periosteal reactions are located primarily on the concave aspect of long bones. Pulmonary osteoarthropathy is the best example. These reactions are not densely ossified and are associated with

benign or malignant tumors of the thoracic cavity (Fig. 6). The mechanism of growth is unknown, but after thoracotomy (with or without removal of tumor) the reaction subsides within 6 months.

Dense, elliptic periosteal reactions vary from 2 mm. to 1 cm. in thickness. The elliptic periosteal reactions are thickest near the center; they taper towards both ends (Fig. 7, 8, 9 and 10). They are present in longstanding cortical osteoid osteomas. Occasionally, round cell tumors (Ewing's tumor or reticulum cell sarcoma) treated by irradiation may cause elliptic reactions. In the latter, however, the elliptic reaction is permeated by osteolytic areas which are characteristic of malignant growth.

Periosteal cloaking is found in longstand-



FIG. 11. Periosteal cloaking due to Gaucher's disease. Notice the rather straight borders and the elevation of the periosteum from the host bone. (*A*) Standard roentgenogram. (*B*) Magnified roentgenogram.

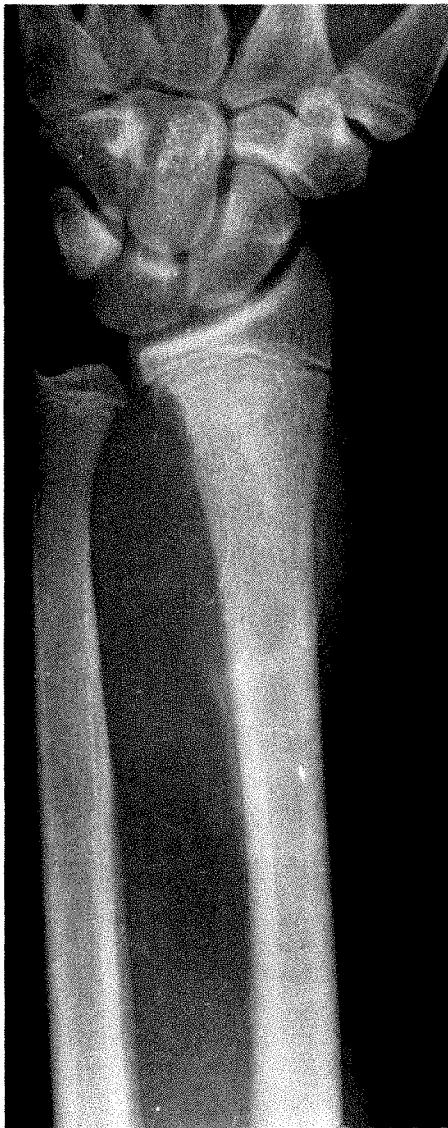


FIG. 12. Codman's triangle due to hemorrhage. Note the erosion of the distal end of the radius and the presence of a Codman's triangle on the medial aspect of the radius. This was considered a malignant tumor but eventually proved to be hematoma. Codman's triangle occurs with benign and malignant lesions.

ing benign conditions such as storage disease and chronic osteomyelitis. It is usually several millimeters thick and irregularly dense. The free margin is straight (Fig. 11, *A* and *B*). It does not occur with malignancy.

Codman's triangle was first described by Ribbert in 1914, who believed it was due to

periosteal elevation caused by an expanding mass.

The significance of the triangular *Codman's cuff* merits particular mention. Long considered a manifestation of malignant bone disease, it is now appreciated that it may result by anything lifting the periosteum, be it benign or malignant (Fig. 12 and 13). Microscopically, tumor cells are not present within the cuff. Indeed, when invaded by tumor, Codman's triangle disappears. In contrast, collections of pus and blood notoriously elevate periosteum, producing these periosteal triangles.

2. INTERRUPTED PERIOSTEAL REACTIONS

The *interrupted periosteal reactions* are not uniform. They are pleomorphic with

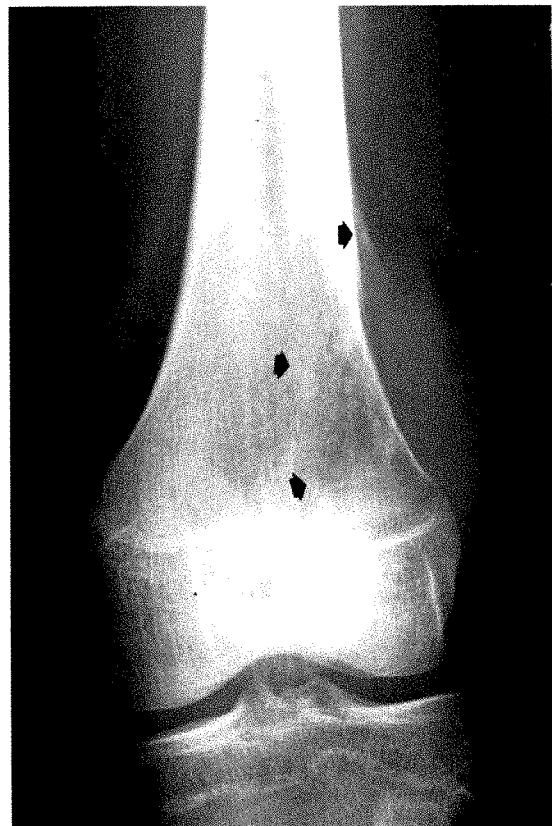


FIG. 13. Codman's triangle secondary to osteosarcoma. A Codman's triangle is noted at the proximal end of an osteolytic lesion in the distal end of the femur. Codman's triangle is frequently present with malignant tumors but may be present with benign conditions.

varying roentgen patterns. Lamellated (onion skin) or perpendicular (sunburst) periosteal reactions are classic examples. Caused by periosteal elevation in active conditions (malignant tumor, infection, repeated hemorrhage), the interrupted pattern indicates an active rapidly progressive process.

Characteristic of interrupted periosteal reactions is their lack of stability; roentgenographically, they change constantly. The more aggressive the irritant, the greater the degree of periosteal change from week to week. Sometimes, even days suffice for these changes to become apparent.

Lamellated periosteal reactions occur in active conditions such as acute osteomyelitis and malignant tumors. The lamellations are due to intermittent growth. According

to Sisson,³ single lamellations may form within 1 week. Brunschwig and Harmon² believe that the lamellations are the result of alternating periods of rapid and slow growth. During the slow growth, the periosteum has time to form a layer of bone analogous to the involucrum of infection. During rapid growth no new bone is formed. Bleeding into the periosteum, too, influences these roentgen appearances (Fig. 14, *A* and *B*).

Perpendicular (sunburst) reactions are the result of new bone growing at right angles to the shaft of host bone (Fig. 15, *A* and *B*; 16; and 17). Usually, they are caused by a malignant tumor which elevates the periosteum. In Brunschwig and Harmon's² opinion the new bone formation lies along fibrous bands (Sharpey's fibers) which ex-

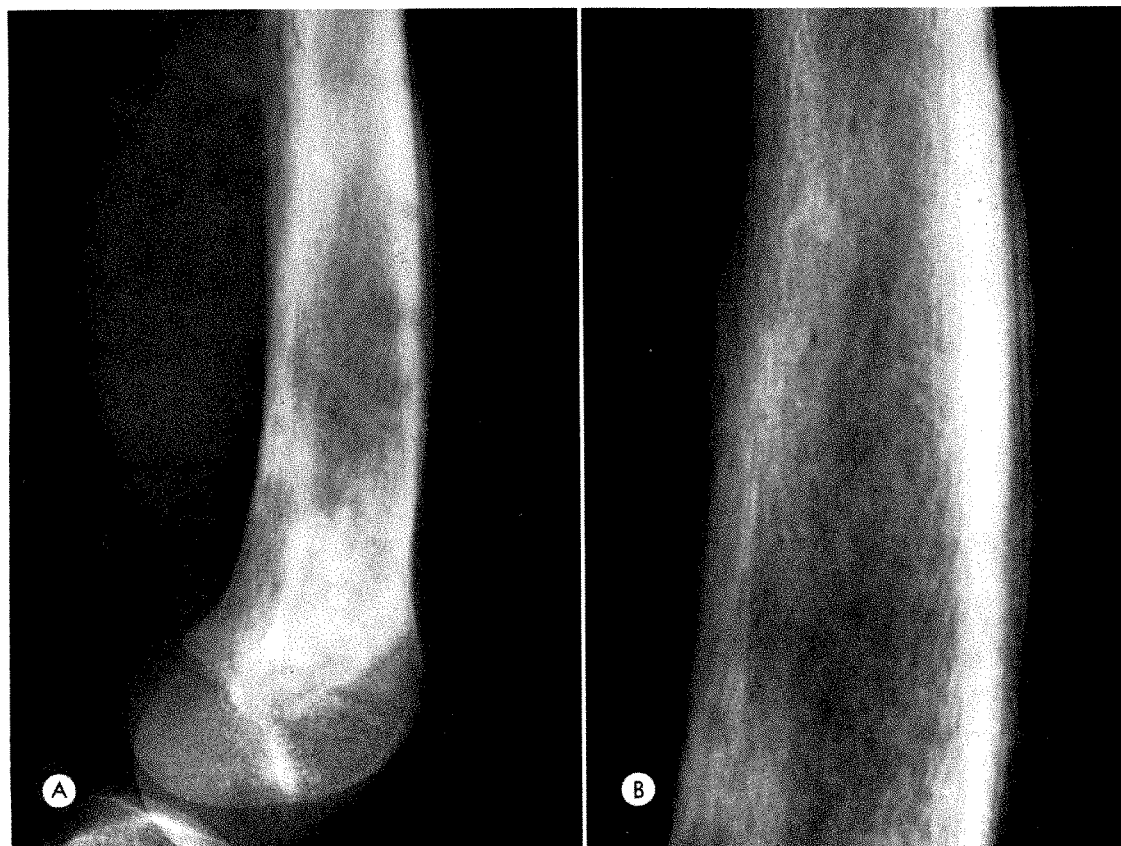


FIG. 14. Lamellated periosteal reaction secondary to osteosarcoma. There is a large destructive area within the distal end of the femur. The periosteal reaction on the anterior surface is layered. (*A*) Standard roentgenogram. (*B*) Magnified roentgenogram.



FIG. 15. Perpendicular (sunburst) periosteal reaction due to osteosarcoma. There is marked destruction in the distal end of the femur with considerable soft tissue extension. Notice that in the inferior portion of the soft tissue extension, posteriorly, there are perpendicular densities radiating from the bone. (A) Standard roentgenogram. (B) Magnified roentgenogram.

tend between periosteum and cortex. Blood vessels, too, run between periosteum and cortex; very likely perpendicular bone growth also takes place along these vascular channels.¹ Microroentgenography as well as serial histopathologic sections support this concept.

Osteosarcomas and Ewing's tumor tend to stimulate "sunburst" reactions. Chondrosarcomas and fibrosarcomas show much less periosteum activity. At times, Ewing's tumor and osteosarcoma will elevate the periosteum without provoking reaction.

Amorphous reactions. Malignant tumors, in addition to causing lamellations and perpendicular striations (with or without interspersed deossified areas), often reveal amorphous calcific densities (Fig. 18). Lying mainly between periosteum new bone and its parent bone cortex, these amorphous deposits may present extension of tumor bone rather than periosteal response to the tumor. Often oval or spherical in shape, they vary in size from millimeters to centimeters in cross sections. These amorphous deposits usually denote bone malignancy.

Rarely do they accompany benign bone tumors. Usually, they help differentiate primary from metastatic bone tumors, the latter being far less likely to cause periosteal reactions or extraosseous amorphous deposits unless an associated pathologic fracture is present.

Some malignant bone tumors tend to provoke more periosteal reaction than others, a difference not related to the degree of periosteal elevation. Fibrosarcomas notoriously peel the periosteum a considerable height from parent bone, yet they produce little periosteal new bone formation. The microscopic evidence suggests that a periosteal response does occur which is destroyed al-



FIG. 16. Perpendicular (sunburst) periosteal reaction due to osteosarcoma. There is a large tumor in the distal end of the femur with a Codman's triangle on the posterior aspect and lamellated periosteal reaction anteriorly.



FIG. 17. Perpendicular (sunburst) reaction of the fourth metacarpal due to Ewing's sarcoma. Extensive destruction is noted in the fourth metacarpal. Perpendicular periosteal reaction extends on both sides of the metacarpal.

most as soon as it forms. This is true also of chondrosarcomas. In contrast, osteosarcoma and Ewing's tumor seem to stimulate new bone formation. It is but fair to recall that sometimes osteosarcoma and Ewing's tumor, though they elevate the periosteum, may not provoke demonstrable periosteal new bone response. Perhaps rate of tumor growth explains the difference.

In general, the following train of thought may reasonably be applied to bone lesions with particular reference to the periosteum.



FIG. 18. Amorphous deposits of tumor new bone and extensive destruction of the neck of the femur due to osteosarcoma. The small deposit of amorphous calcification is often present with malignant bone tumors. It probably represents a deposit of tumor new bone rather than periosteal reaction.

Osteoblastic lesions confined to the host bone, unattended by changes beyond the bone, may be benign or malignant. If interrupted periosteal new bone is manifest beyond the parent bone, in the absence of infection or trauma, the lesion is far more likely to be a primary bone malignancy

than metastatic (unless the primary lesion is of bone origin). Solid periosteal new bone usually proves to be due to a benign process.

SUMMARY

1. Periosteal reactions occur in a variety of bone diseases and may be useful in differentiating among these conditions.
2. Solid reactions are seen in benign conditions and are useful in differentiating eosinophilic granuloma and osteoid osteoma from malignant bone tumors (Ewing's tumor).
3. Interrupted periosteal reactions are common in active, progressive disease which may be either neoplastic or inflammatory. The lamellated type is associated with both neoplasm and infection, while the perpendicular type is more common in neoplastic conditions and rare with infection.
4. Codman's triangle is due to elevation of the periosteum and not necessarily to malignancy.

Jack Edeiken, M.D.
Jefferson Medical College Hospital
Philadelphia 7, Pennsylvania

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EOSINOPHILIC GRANULOMA OF BONE*

EXPERIENCE WITH 20 CASES

By SEYMOUR FISKE OCHSNER, M.D.

NEW ORLEANS, LOUISIANA

EOSINOPHILIC granuloma of bone is especially interesting to radiologists because it occurs in any part of the skeleton and presents a wide variety of appearances. It is a benign process, but sometimes the roentgenographic picture is so similar to that of a malignant tumor that neoplastic disease must be considered in differential diagnosis. Although it was classified as a distinct entity only recently, eosinophilic granuloma has an interesting history. This report will review the background of our present concept of the disease, record some information from previously reported cases, and review experience at the Ochsner Clinic with 20 patients seen during a period of 20 years ending December, 1965.

HISTORICAL REVIEW

The term "eosinophilic granuloma" was introduced in 1940 by Lichtenstein and Jaffe,¹² who reported a case of a solitary tumor of the femur. The same issue of the same journal contained an article on the same disease by Otani and Ehrlich,¹⁴ who referred to their cases as solitary granulomas of bone. Only 2 years later, Green and Farber⁸ reported 10 cases of eosinophilic granuloma, some of which were in patients with multiple lesions. They stressed that eosinophilic granuloma of bone, Hand-Schüller-Christians' disease, and Letterer-Siwe's disease were various manifestations of a similar pathologic process. More recently, these lesions have come to be known as reticulosis, reticulo-endotheliosis, or histiocytosis.¹¹

In addition to the evolving concept of an underlying unity of these various osseous manifestations, reports have shown that other nonskeletal organs or systems may contain similar eosinophilic granulomatous

masses. Arnold¹ reported eosinophilic granuloma of bones with associated pulmonary involvement. In 1952, Lackey and associates¹⁰ reported cases of eosinophilic granuloma limited to the lung. In 1951, Booher and Grant² collected 11 cases of gastric granulomas and noted that they usually involved the antrum of the stomach and tended to grow from submucosal nodules into polypoid masses.

It is the relatively frequent involvement of the skeletal system, however, that gives the disease its chief importance. Apparently, any bone in the body may be affected, but most lesions are found in the skull, ribs, spine, or long bones.

PATHOLOGIC FINDINGS

In their initial report, Lichtenstein and Jaffe¹² described the pathologic alterations so accurately that little has been added since. They described the tumor as a "localized, single lesion, starting in the medullary cavity and tending to erode, expand and perforate the cortex in the bony site affected." The mass may extend into the neighboring soft tissues and "the roentgenographic and clinical findings may lead one to suspect the presence of a malignant bone tumor. Surgical exploration shows that the affected portion of the bone has been extensively replaced by a more or less soft, yellowish or brownish tissue." The microscopic appearance is "characterized essentially by the presence of compacted, tumor-like aggregates of large phagocytic cells, with conspicuous collections of eosinophilic leukocytes interspersed." In addition, they reported "an appreciable number of large multinucleated (giant) cells." They stated that this type of lesion previously had been "regarded provisionally as a

* Chairman's address, Southern Radiological Conference, Jan. 29, 1966, Point Clear, Alabama.
From the Department of Radiology, Ochsner Clinic, New Orleans, Louisiana.

peculiar, inflammatory granulomatous lesion of indeterminate nature."

In 1941, Farber⁷ presented his concept that eosinophilic granuloma is one of a group of related granulomatous diseases, including Hand-Schüller-Christian and Letterer-Siwe disease. It is interesting to notice, in retrospect, that in the discussion of Farber's paper, Lichtenstein, Jaffe, and Otani individually expressed disagreement with this concept. Nevertheless, Farber's theory has been generally accepted. Indeed, by 1953, Lichtenstein¹¹ espoused the idea completely and introduced the term "histiocytosis X," to specify the common pathologic denominator. He suggested that the disease is a specific inflammatory histiocytosis. Eosinophilic granuloma was considered the localized form, Letterer-Siwe disease the acute or subacute disseminated form, and Hand-Schüller-Christian disease the chronic disseminated form. Dundon and co-workers⁵ pointed out that in an early phase of development, these lesions may undergo partial liquefaction and appear as a cystic mass.

In a more recent discussion, Jaffe⁹ expressed the opinion that eosinophilic granuloma has little relationship to xanthogranuloma and heals by resolution (if it heals) and not by conversion into a xanthomatous lesion. He also stated that solitary osseous lesions in Hodgkin's disease may be difficult to differentiate cytologically from eosinophilic granuloma.

INCIDENCE

Most reports of eosinophilic granuloma stress the frequency of the disease in young persons.⁵ Sbarbaro and Francis,¹⁶ for instance, reported that 34 per cent of 50 patients were younger than 4 years old and 74 per cent were younger than 20 years of age. Although most of the patients in the present series also were young, 2 patients were 45 years old, so that this disease must be considered in the middle-aged patient with an osteolytic lesion of bone.

The incidence according to sex varies in reported series. Fifteen of our 20 patients

TABLE I
SKELETAL SITE IN 20 PATIENTS WITH EOSINOPHILIC
GRANULOMA OF BONE

Site	No. of Cases
Skull	6
Rib	3
Spine	3
Mastoid	2
Pelvis	2
Femur	2
Mandible	1
Humerus	1

were females. Most patients seen at the Ochsner Clinic are white; only 1 of the patients in our series was a Negro. Sbarbaro and Francis¹⁶ considered it significant that all 50 cases at Memorial Hospital in New York occurred in the white race.

CLINICAL MANIFESTATIONS

These patients have few, if any, constitutional symptoms. The osseous lesion usually causes localized pain, so that the original clinical diagnosis revolves around the question of the possible causes of pain in a particular anatomic area. Some patients have a palpable mass, as well as localized pain. Fever, elevation of erythrocyte sedimentation rate, and leukocytosis with relative eosinophilia are rare and not ordinarily helpful in diagnosis.

The skeletal sites in our 20 cases are shown in Table I. The skull, ribs, and spine were the most common sites.

ROENTGENOGRAPHIC OBSERVATIONS

The essential lesion is identified by roentgenographic examination. In essence, the granuloma produces a localized area of rarefaction in the diseased bone. This radiolucency starts in the medullary region. As it expands, it progressively erodes the inner side of the denser cortical bone, producing a smooth, irregular, or scalloped defect in the inner cortical profile. The involved cortex becomes progressively thinner, and the radiolucent medullary defect progres-

Ribs. Three of our patients had granulomas of a rib. All 3 were older than 35 years of age. Each had a slightly painful, solitary osteolytic lesion and a pathologic fracture (Fig. 4). In each, the initial fear was that metastatic carcinoma was the cause. There is nothing characteristic about these radiolucent lesions.

Pelvis. Surprisingly large osteolytic areas may be present in the pelvis. The lesion usually has sharply defined borders, but they may appear irregular or scalloped, and inner bony ridges may produce a somewhat trabeculated appearance (Fig. 5, *A* and *B*). The lesion may look spongy or like a "soap bubble." In our patients, the roentgeno-

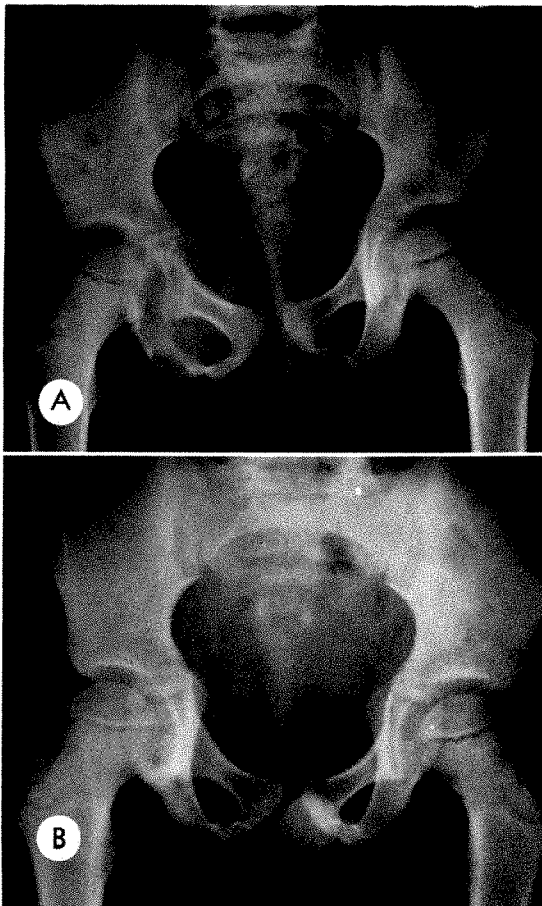


FIG. 5. (*A*) Eosinophilic granuloma in right ischium produces a large, irregular area of osseous destruction. (*B*) Improvement after biopsy and radiation therapy.

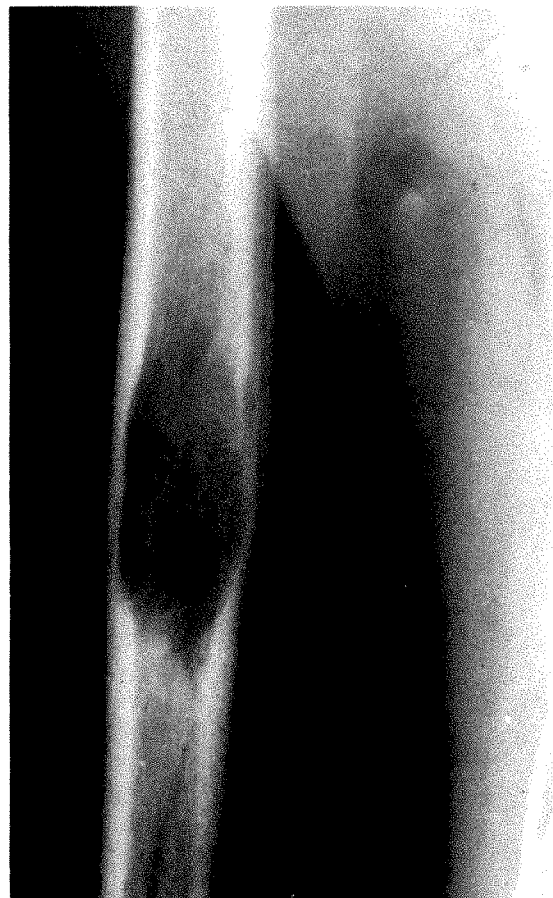


FIG. 6. Radiolucent eosinophilic granuloma of humeral diaphysis with periosteal reaction. Ewing's tumor was a differential diagnostic problem.

graphic appearance improved after radiation therapy.

Long Bones. Of the eosinophilic granulomas involving the long bones, those of the femur are most frequent. Among reported cases, roentgenograms of the femur present some of the most bizarre and challenging appearances. Simple osteolytic lesions may suggest bone cyst or sarcoma of bone. Jaffe⁹ noted that bone cysts usually are oriented to the end of the diaphysis, and are larger and less painful than granulomas. Relatively long lesions in eosinophilic granuloma may suggest fibrous dysplasia, and destructive lesions with adjacent sclerosis may suggest osteomyelitis. Those with surrounding periosteal reaction may mimic Ewing's sarcoma, especially in the



FIG. 7. Round radiolucent area in lower left femoral epiphysis: a rare site of eosinophilic granuloma.

earlier phases of the tumor, and Jaffe⁹ suggested that some "cured" cases of Ewing's tumor may have, in truth, been eosinophilic granulomas. In a 9 year old girl in our series, the humeral eosinophilic granuloma mimicked Ewing's sarcoma (Fig. 6). Simple curettage resulted in complete cure.

Young persons are frequently affected and so the differential diagnosis of malignant bone tumor is a genuine problem. The tragedy of amputating an extremity for a localized benign tumor can be avoided only if the possibility of eosinophilic granuloma is kept in mind when the differential diagnosis of bone lesion is under consideration.

Epiphyses. In one of our patients, a 4 year old boy, an eosinophilic granuloma involved the lower femoral epiphysis (Fig. 7). Apparently, the epiphyses are rarely affected, as this site was not encountered in 2 of the largest reported series of cases.^{13,16} In our patient, a round, radiolucent lesion occurred in the center of the epiphysis. After curettage, through a transmetaphyseal approach, the lesion healed and normal epiphyseal growth continued (Fig. 8, *A* and *B*). If the disease is not recognized and treated, the epiphysis probably would collapse and produce deformity of the articulating surface.

Lung. After the first reports that pulmonary lesions could occur in patients with eosinophilic granuloma, Farinacci and co-workers⁶ described similar lesions in persons who did not have osseous manifestations.

The lesions have been a mixture of stippled or finely nodular opacities, combined with reticular and patchy infiltrations. Sometimes small, cyst-like shadows give the lung a honeycombed appearance. In only one of our patients was pulmonary disease manifest. The lesions later cleared and the lungs assumed an essentially normal appearance.

Gastrointestinal Tract. None of our pa-



FIG. 8. Epiphyseal eosinophilic granuloma (same as Fig. 7). (*A*) Surgical transmetaphyseal approach. (*B*) Essentially normal appearance 4 years later.

tients had gastrointestinal granuloma. Rigler *et al.*¹⁵ presented 9 cases with roentgenograms illustrating isolated polypoid lesions of the stomach.

DISCUSSION

Although multiple lesions may occur in one patient, and despite the similar histopathologic appearance of eosinophilic granulomas and other reticulososes, such as Hand-Schüller-Christian and Letterer-Siwe diseases, we would perhaps be wise to maintain an open mind regarding the degree of underlying similarity of these diseases. After a recent review of a relatively large group of cases, for example, McGavran and Spady¹³ could find no patients whose disease progressed to a more complex form. Until the cause of the disease is discovered, therefore, they believed that doubt must remain about the extent of relationship between this group of diseases.

One of our patients had successive lesions in the mandible and mastoid in a 3 year interval. None of the others in this series had any evidence that the disease would progress to other than solitary osseous lesions.

The importance of prompt recognition and careful treatment is indicated by the tragic complication of permanent paralysis that resulted from damage to the spinal cord which followed sudden collapse of the involved thoracic vertebra in one of our patients.

TREATMENT

Relatively conservative management is undoubtedly desirable. Biopsy for diagnosis can be readily followed by simple curettement, or small lesions may be excised at biopsy. Roentgen-ray therapy has been used to relieve pain or promote healing. Favorable results have been reported after doses as small as 500 to 1,500 rads.³ In our series, radiation therapy seemed particularly useful in patients with mandibular, vertebral, and pelvic lesions, in doses of 600 to 1,000 rads. McGavran and Spady¹³ concluded that the lesions healed regardless of

the type of treatment, including several patients who had no specific treatment.

SUMMARY

Eosinophilic granuloma of bones is of special interest to radiologists because it is first identified in roentgenograms and may mimic many benign and malignant conditions. Since this entity was first described 26 years ago, it has been reported in many skeletal locations. In our 20 cases, the skull, ribs, and spine were the most frequent sites; an unusual site in the femoral epiphysis is recorded. Local pain and disability are the usual symptoms, but vertebral granulomas may damage the spinal cord, and pathologic fracture of long bones may occur. Correct diagnosis usually requires biopsy. Results of conservative treatment are good; it is important not to overtreat this benign tumor in the fallacious assumption that it is a malignant tumor. The most frequently advocated treatment is curettage, with or without postoperative radiation therapy in moderate dosage.

Department of Radiology
Ochsner Clinic
1514 Jefferson Highway
New Orleans, Louisiana

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ADAMANTINOMA OF LIMB BONE* MALIGNANT ANGIOBLASTOMA

By ROBERT S. ROSEN, M.D.,† and C. PETER SCHWINN, M.D.‡
LOS ANGELES, CALIFORNIA

ADAMANTINOMA (malignant angio-blastoma) of limb bone has been recorded approximately 40 times in the world literature, making it one of the rarer primary bone neoplasms. Until 1942 the tumor was referred to as "adamantinoma of the tibia," because the first 17 reported cases occurred exclusively within the tibial shaft. Since that time there have been sporadic reports of its appearance in the ulna, femur, fibula and radius.^{1,2,3,9}

The case reported below is unique not only because of its location and unusual histopathology, but because of the angiographic features of adamantinoma.

REPORT OF A CASE

J.R. (244-04-75), a 16 year old female patient, was admitted to Los Angeles County General Hospital complaining of intermittent pain in the left knee of 1 year's duration. Six months prior to admission, a thigh mass was discovered during a routine pre-school examination. At that time, permission for biopsy could not be obtained.

On admission, physical examination was entirely negative except for the left thigh area. A firm, slightly tender, nonmovable mass was palpable along the medial aspect of the left thigh. The mass measured 7×5 cm. and was associated with atrophy of the proximal thigh muscles. The overlying skin was normal and no significant lymphadenopathy was present. All laboratory studies were normal.

Roentgenograms of the left femur showed a well circumscribed cystic lesion within the mid-portion of the femoral shaft (Fig. 1). Subperiosteal new bone was deposited along the cortical margins of the tumor and there was a probable overlying soft tissue mass. A percutaneous femoral arteriogram demonstrated tumor vessels within the cystic intra-osseous portion of the tumor (Fig. 2). In addition, there was a well de-



FIG. 1. Roentgenogram of the femur shows a cystic slightly expansile tumor within the mid-portion of the shaft. Faint subperiosteal new bone is deposited along the lateral cortical surface.

* From the Los Angeles County General Hospital and University of Southern California.

† Department of Radiology.

‡ Department of Pathology.



FIG. 2. In the early arterial phase, a localized medial deviation of the superficial femoral artery is seen opposite the tumor. The terminal branches of the profunda femoral artery are displaced by a mass.

finer vascular soft tissue mass contiguous with the periosteum of the femoral shaft (Fig. 3, *A* and *B*).

An open biopsy revealed a soft friable tumor mass covered by an intact shell of periosteum. Sections of both the intramedullary and soft tissue components were interpreted as adamantinoma. Amputation was advised but refused. At the present time the patient is under the care of her private physician.

PATHOLOGIC FINDINGS

The histopathologic findings were unique. In certain areas (Fig. 4) the pattern was distinctly glandular or tubular. At higher magnification (Fig. 5), cuboidal or columnar lining cells were separated from a sparse, highly vascular stroma by a basement membrane. In other areas, sheets of apparently epithelial elements were arranged without discernible pattern and exhibited a meager stroma connective tissue network (Fig. 6). In none of the sections was a significant fibroblastic component noted.

These unusual histologic features were commented upon by several consultants. Dahlin⁵ stated "The diagnosis I favor is adamantinoma. I hasten to add that the atypical location makes this a difficult diagnosis to accept, especially since the histology is not ordinary for adamantinoma. I can't ignore the epithelial look of this tumor, but it's being a metastasis seems unlikely." Lichtenstein¹⁰ stated "My own impression is that . . . of an epithelial tumor metastatic to bone, although I would not venture to pinpoint the primary site . . . in many places one sees cords or columns of cells and suggestive alveolar formations." Stewart¹³ expressed the opinion "I don't think this is a metastatic tumor . . . this reminds me of two things; first the pattern in parts of those lesions usually called adamantinoma . . . and second, the occasionally rare and so-far unnamed tumor, which is erroneously diagnosed as metastatic, resembling in varied areas patterns confused with bronchogenic cancer all the way over into dysgerminoma."

In spite of the absence of a significant fibroblastic component, we have classified this tumor as adamantinoma (malignant angioblastoma), realizing that it may be as Stewart suggests a "so-far unnamed tumor."

DISCUSSION

Fischer⁷ in 1913 first recognized adamantinoma of the tibia as a separate entity, and because of its significant epithelial component speculated that it arose as a result of

abnormal embryonal invagination of fetal epithelium within bone. Ryrie¹² in 1932, although still in agreement as to its epithelial origin, suggested that the lesion arose from traumatic implantation of the skin layer or its appendages into the periosteum of the tibial shaft. Hicks⁸ reported 2 cases of adamantinoma in 1954 which he felt exhibited synovial rather than epithelial differentiation. He considered these tumors to be frank synovial sarcoma rather than some misplaced epithelial remnant. Changus *et al.*⁴ reviewed 8 cases of tibial adamantinoma and concluded that they were of vascular rather than epithelial origin. They proposed that the tumor was derived from primitive mesenchymal cells,

i.e., angioblasts, and that the term adamantinoma was a misnomer. They suggested instead that this tumor be referred to as malignant angioblastoma.

The review of sections from this case was made in conjunction with 5 other cases of adamantinoma made available to us from the consultation files of the California Tumor Tissue Registry. In addition, one of the authors (C.P.S.) has reviewed the cases reported by Changus *et al.* These experiences, augmented by a review of the literature, have led us to conclude that: (1) adamantinoma is probably of angioblastic origin; (2) when adequate numbers of representative sections are available, transitional zones can be found between angio-

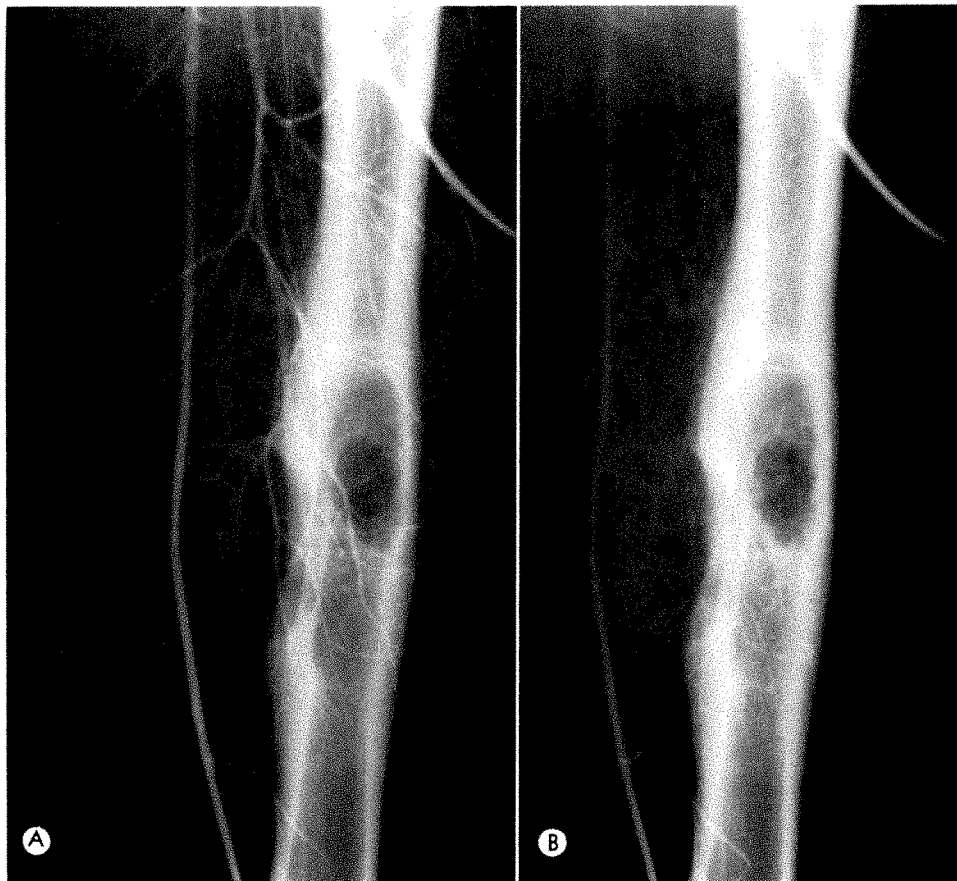


FIG. 3. (A) Late in the arterial phase a well defined vascular soft tissue mass apparently contiguous with the periosteum appears. (B) During parenchymal staining, abnormal vessels are seen within this soft tissue mass. In addition, the cystic intra-osseous portion of the tumor develops a vascular blush. Questionable sinusoid formation is seen within the intramedullary portion.

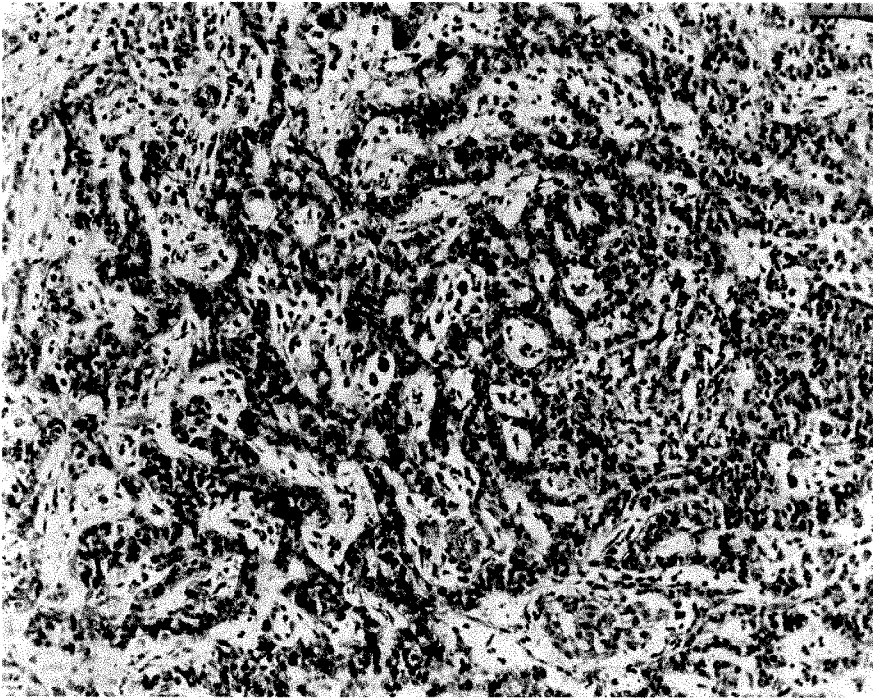


FIG. 4. The predominant pattern in this portion of the tumor is glandular or tubular. The stroma is highly vascular (75 $\times$).

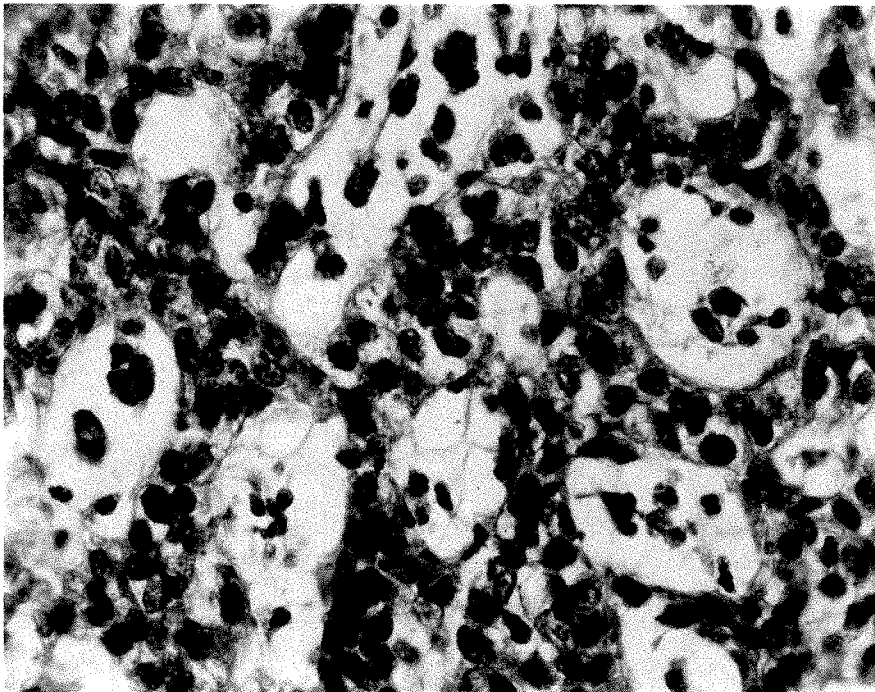


FIG. 5. Higher magnification again shows this pseudoglandular pattern of cuboidal or columnar cells separated from the stroma by a basement membrane (500 $\times$).

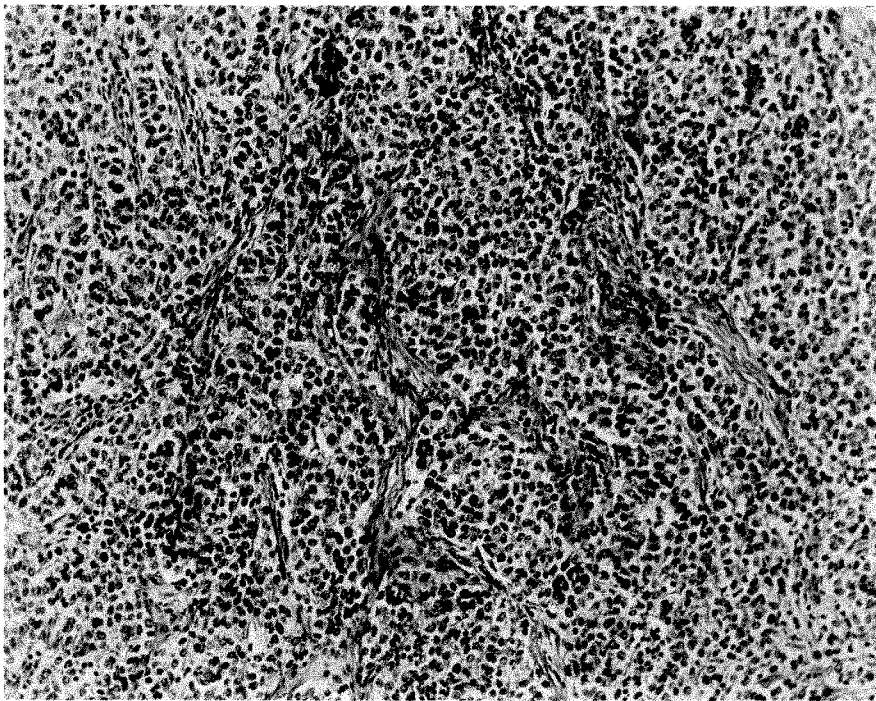


Fig. 6. There is a haphazard arrangement of epithelial-like elements exhibiting a meager collagenous stromal component. The sheets of cells are arranged without any discernible pattern (75 $\times$).

blastic proliferation, endothelial lined blood spaces and pseudoepithelial cell masses; (3) the majority of malignant angioblastomas show considerable fibroblastic proliferation; and (4) sections from different areas in a single tumor may resemble either ameloblastoma or synovial sarcoma.

The clinical behavior of adamantinoma is uncertain. The tumor develops insidiously and slowly and tends toward progressive local invasion.⁹ Thirty per cent of the recorded cases show metastases.² Naji *et al.*¹¹ have recently described a case in which there were massive bilateral pulmonary and lymph node metastases at autopsy. The roentgenographic appearance is almost always that of a well circumscribed cystic lesion within a limb bone (Fig. 1). The bone, commonly tibia, is expanded and shows varying amounts of cortical destruction, periosteal reaction and a soft tissue mass. All of these features were present in this case.

Percutaneous femoral arteriography was performed in an attempt to evaluate the

vascular pattern and extent of the tumor. In the early arterial phase, there was displacement of the terminal branches of the profunda femoral artery about a soft tissue mass (Fig. 2). This well defined vascular soft tissue mass was contiguous with the periosteum and was best seen in the late arterial and parenchymal phases (Fig. 3, *A* and *B*). Tumor vessels, abnormal both in number and extent, supply this soft tissue component. The cystic intra-osseous portion of the neoplasm also showed a marked increase in vascularity. Abnormal vascular channels, presumably tumor vessels, were seen within the areas of greatest bone destruction. The correct histologic diagnosis was not predicted on the basis of this examination. It was felt, however, that the combination of subperiosteal new-bone formation with probable rupture through the periosteum, abnormal vessels within the osseous portion of the tumor and a vascular soft tissue mass strongly suggested the presence of a malignant tumor.

The prognosis in adamantinoma is uncer-

tain. The long-term follow-up of 27 cases revealed local recurrence in 16 of 27 and biopsy proven metastases in 4 cases.⁸ These figures clearly indicate that adamantinoma is a formidable tumor, prone to local recurrence, given to distant metastases and that it is best treated by complete local resection or amputation.

SUMMARY

A case of adamantinoma of the femur is reported. Its controversial and sometimes bizarre histopathology is discussed. Both the plain roentgenographic and arteriographic features of the tumor are reviewed.

Robert S. Rosen, M.D.
Department of Radiology
Los Angeles County General Hospital
1200 North State Street
Los Angeles, California 90033

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BENIGN PROLIFERATIVE SKIN LESIONS CAUSING DESTRUCTIVE AND RESORPTIVE BONE CHANGES

By GEORGE B. GREENFIELD, M.D.,* WILLIAM ROSADO, M.D.,† and
FRITZ ROTHBART, M.D.‡
CHICAGO, ILLINOIS

HYPERKERATOSIS and verrucae of the so-called "mutilating" type can cause bone destructive and erosive lesions in the extremities. These entities should be

considered in the differential diagnosis of a lesion in the bones of the hands or feet.

Hyperkeratosis is a skin condition in which the horny layer of the skin is aug-



FIG. 1. Case 1. (A and B) Soft tissue irregularity involving the left great toe. The proximal phalanx shows smooth tapering. The distal phalanx is markedly thinned. There is definite cortical destruction at the lateral aspect of the distal phalanx.

* Assistant Director, Diagnostic Radiology, Cook County Hospital, Chicago, Illinois; Clinical Assistant Professor of Radiology, University of Illinois Medical School, Chicago, Illinois.

† Former Resident in Radiology, Cook County Hospital, Chicago, Illinois.

‡ Chief of Radiology, American Hospital, Chicago, Illinois.



FIG. 2. Case I. Transmetatarsal amputation. A large irregular soft tissue mass is seen at the anterior aspect and another at the plantar aspect of the amputation stump.

mented. This may come about by increased proliferation of cells.² Verrucae, or warts, are tumor-like structures which develop in the skin and mucous membranes as a result of invasion of a virus.¹

REPORT OF CASES

CASE I. A 20 year old Negro male presented with a fungating mass on the sole of the left foot. Roentgenograms (Fig. 1, *A* and *B*) were obtained on December 22, 1961.

He had been admitted 2 years previously for the same reason. At that time excision of the lesions deep to the plantar fascia was performed and the area was covered by skin grafts.

Pathology. The specimen consisted of an irregularly shaped, approximately 1 cm. in diameter, partly friable, brown tissue fragment. Microscopically, the section revealed a thick keratin layer and blood overlying wide squamous epithelium and scant subjacent stroma with some congestion and chronic inflammatory cells. The diagnosis was hyperkeratosis.

A left transmetatarsal amputation was performed in December, 1961.

The patient returned with recurrence at the amputation site in October, 1962 (Fig. 2) and a left below-the-knee amputation was performed. Subsequently, he developed involvement of the right foot and both hands.

CASE II. A 45 year old white female presented extensive growths involving her hands and feet, which had been present for many years, and which she had been trimming with a razor blade. She was employed in a circus side-show, exhibiting her extremities. A clinical diagnosis of warts was made. She refused any treatment and was lost to follow-up (Fig. 3, 4 and 5).

DISCUSSION

Both cases showed bone thinning and resorptive changes; in Case I definite cortical destruction was present. The former



FIG. 3. Case II. Right hand. Extensive soft tissue proliferation of thumb and distal middle finger. There are bone resorptive changes at all distal tufts.

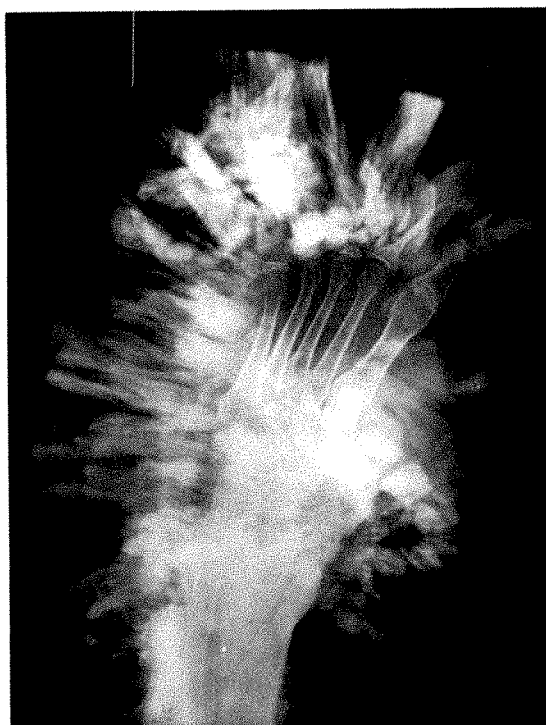
FIG. 5. Case II. Foot. Massive soft tissue proliferation and tapering of the distal phalanges. Marked thinning of the proximal phalanges and resorption of the major portions of the proximal phalanx of the fifth toe.



changes must be differentiated from neurotrophic changes from other causes. The marked soft tissue proliferation would, however, establish the diagnosis. Cortical destruction from metastases or primary tumors could cause some difficulty in the diagnosis; however, when cortical destruction is combined with bone thinning and resorption, the diagnosis of a benign pro-



FIG. 4. Case II. Left hand. Massive soft tissue proliferation is noted, as well as luxation at the first metacarpophalangeal joint.



liferative skin lesion should be considered. The differential diagnosis is discussed.

SUMMARY

Two cases of benign proliferative skin lesions causing bone changes are reported.

George B. Greenfield, M.D.
Cook County Hospital
Chicago, Illinois 60612

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ARTHROGRAPHY OF THE KNEE BY DOUBLE CONTRAST METHOD*

By ROBERT H. FREIBERGER, M.D., PAUL J. KILLORAN, M.D.,
and GONZALO CARDONA, M.D.
NEW YORK, NEW YORK

ARTHROGRAPHY of the knee is a safe and technically simple procedure permitting accurate diagnosis of lesions of the menisci, particularly tears. While the accuracy of clinical diagnosis among experienced surgeons is high, tear of the meniscus is a common lesion and there are a significant number of cases with equivocal or atypical clinical findings. In these particularly, a graphic means of demonstrating the meniscus is of value.

METHODS

In the 60 years in which knee arthrographies have been performed, various roentgenographic contrast media have been employed.^{5,6,7,13,14} The only ones found to be useful have been air and other gases and the water-soluble positive contrast media. A combination of the two provides a double contrast study.

Air and the other more quickly absorbed gases are still being used.¹ Their main disadvantage is that with the large quantities which are used, there is uncomfortable distention of the knee as well as the possible hazard of air embolism. One death and one near death from this cause have been reported.^{5,10} The difference in density between the relatively radiolucent cartilage and the surrounding air is not very great and interpretation of roentgenograms can be difficult. Despite previous aspiration, joint effusion may reduce diagnostic accuracy,^{12,15} apparently because the gas does not always displace the residual fluid within meniscal tears. Lindblom,¹¹ comparing air arthrograms with those made with water-soluble positive contrast media, found the percentage of accuracy higher with the latter.

In positive contrast arthrography, relatively small quantities (approximately 10 cc.) of a water-soluble contrast agent are used. This method has been found safe and accurate and large series of cases have been reported and analyzed.^{8,9,11,16} During the early development of this method, the available contrast agents caused synovial irritation and pain;^{6,13} however, urographic media presently used have not produced these complications. One disadvantage is that excess contrast agent drains into the dependent portion of the knee, where it may partly cover and obscure, rather than outline, the meniscus.

The combination of gas and positive contrast substance was first used by Bircher.⁴ Its main advantage is that the meniscus, which is thinly coated by positive contrast agent, is also surrounded by air. Its disadvantages are that, as in air arthrography, large quantities of air may cause embolization and excess contrast agent may obscure portions of the meniscus. These disadvantages were overcome by using a horizontal roentgen-ray beam, as described by Andren and Wehlin.³ This permits the use of small quantities of air (20 to 25 cc.) and positive contrast material (5 to 10 cc.). Excess positive contrast material drains into the dependent portion of the knee and, therefore, away from the portion of the meniscus under examination. Air rises to envelop the part of the meniscus which is being examined. The method should be familiar to radiologists, since it is identical to performing the air contrast barium enema examination in the lateral decubitus position.

We believe that this method, which is described in detail below, provides the best

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From The Hospital for Special Surgery, affiliated with The New York Hospital—Cornell University Medical College.

graphic demonstration of the menisci. Because of the use of small quantities of both air and positive contrast agent, the patient is comfortable and can resume his usual activity as soon as the examination is finished. All methods of arthrography, including the double contrast method described here, demand attention to detail and careful positioning, since correct diagnosis depends upon accurate tangential views and good quality roentgenograms.

EQUIPMENT

1. Sterile tray containing:
 - a. Medicine cup, forceps and gauze pads for skin preparation.
 - b. Drape with central opening.
 - c. Five cc. syringe and No. 25 gauge needle for infiltration of the skin with local anesthesia.
 - d. Twenty cc. syringe and $1\frac{1}{2}$ inch No. 20 gauge disposable needle for the injection of air and opaque material into the joint.
 - e. Ampules of 1 per cent xylocaine and renografin 60 per cent.
2. Lead-shielded film holder with $2\frac{1}{2}$ by 7 inch window to allow 6 exposures on a single 7 by 17 inch film (Fig. 1).
3. Wooden table with plywood top 27 by 16 inches by $7\frac{1}{4}$ inches high to support the leg during examination of the lateral meniscus.
4. Cylindrical cotton pillow 5 inches in diameter, 6 inches long.
5. Aluminum central ray pointer 48 inches long that can be attached to the roentgen-ray tube.
6. Two 7 by 17 inch medium speed screen cassettes.

TECHNIQUE

The patient is placed on the fluoroscopy table so that the knee to be examined is in lateral position and maximally extended. With the aid of the fluoroscope and a metal ruler, a straight line superimposed upon the articular margin of the medial tibial plateau is drawn on the skin (Fig. 2). The patient is then turned to the opposite side and the extremity under examination is

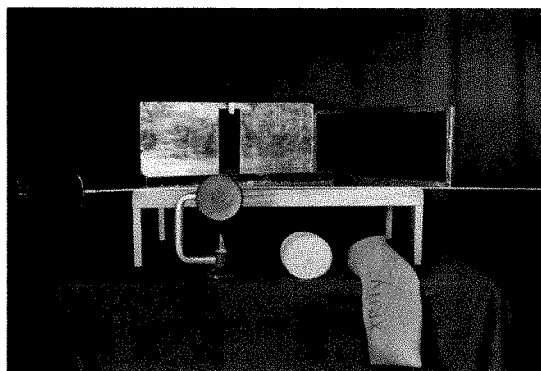


FIG. 1. Equipment used in performing double contrast arthrography. The metal film holder allows 6 exposures of each meniscus on a single 7×17 inch film. The low wooden table supports the leg during the examination of the lateral meniscus. The long aluminum pointer is attached to the roentgen-ray tube to indicate the central beam. The small pillow is placed under the distal femur and the sandbag over the ankle to open the part of the joint being examined.

placed on a low wooden table with the knee in a maximally extended lateral position. A straight line corresponding to the articular margin of the lateral tibial plateau is drawn on the skin (Fig. 3).

The patient then assumes the supine position and a small pillow is placed under the knee. After preparation of the skin with an antiseptic solution, the knee is draped and the skin and subcutaneous tissues are infiltrated with 1 per cent xylocaine at the point where the joint is to be punctured. We prefer the medial approach and insert a disposable $1\frac{1}{2}$ inch No. 20 gauge needle into



FIG. 2. With the aid of the fluoroscope, a line superimposed upon the articular margin of the medial tibial plateau is drawn upon the skin. The knee is maximally extended.

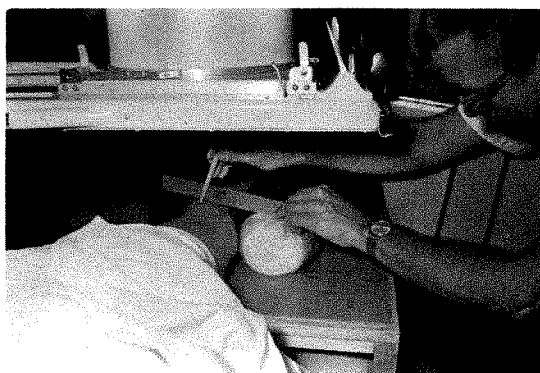


FIG. 3. A line corresponding to the articular margin of the lateral tibial plateau is drawn on the skin.

the sulcus between the patella and the medial femoral condyle at approximately the mid-portion of the patella. If no fluid is present, correct placement of the needle is determined by the ease with which xylocaine can be injected. If synovial fluid is present, as much as possible should be aspirated before the introduction of 20 cc. of air. When the needle is properly placed, air can be injected with only minimal pressure on the plunger of the syringe and usually can be freely aspirated. Five to 10 cc. of renografin 60 per cent is then introduced. The larger quantity is used only if significant residual joint fluid is thought to be present. A small amount of air is injected following the introduction of positive contrast material and the needle is withdrawn. The knee is actively flexed several times, during which a gurgling sensation can be felt and is occasionally heard as the air and fluid flow in and out of the suprapatellar recess. The patient then walks for about 1 minute to ensure adequate distribution of contrast material throughout the knee.

The clinically suspected meniscus is examined first; usually, it is the medial, and for this the patient assumes a prone oblique position. The cylindrical pillow is placed under the lower end of the femur and the columnated roentgen-ray beam is arranged to fall tangential to the posterior aspect of the medial meniscus, which will be uppermost (Fig. 4). The horizontal roentgen-ray beam, its central ray indicated by the alu-

minum pointer attached to the tube, is directed along the line previously drawn upon the skin. The film holder is positioned between the patient's legs so that the window is in the center of the roentgen-ray beam. A sandbag is placed over the ankle to widen the joint space and thus allow a maximum amount of air to surround the contrast-coated meniscus. Six exposures are made, with the leg and patient rotated 30 degrees toward the supine position between each exposure. The central beam is adjusted to follow the slope of the line drawn on the skin. As the more anterior portions of the meniscus are examined, the leg will be flexed at the knee and the sandbag is placed under the heel so that only moderate flexion occurs (Fig. 5).

When the filming of the medial meniscus has been completed, the patient turns to the opposite side into a prone-oblique position for examination of the lateral meniscus. The leg to be examined is placed on the wooden table with the posterolateral aspect of the knee uppermost (Fig. 6). The pillow is inserted under the distal femur and the sandbag placed over the ankle. The film holder is positioned behind the knee and the central beam again is directed along the skin line previously drawn. Six views of the lateral meniscus are obtained with the knee turned 30 degrees between each exposure from the prone-oblique to the supine-

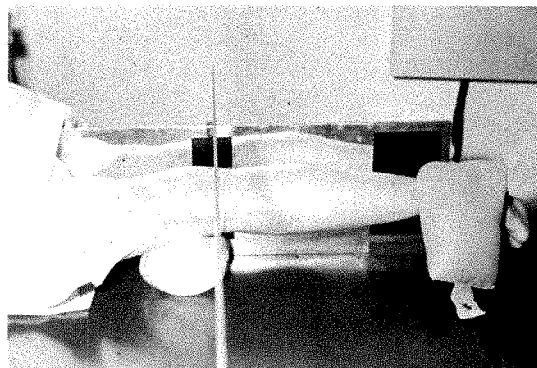


FIG. 4. Initial exposure of the medial meniscus. The patient is in a prone-oblique position so that the posterior portion of the meniscus, which is to be examined, is uppermost. The central beam, indicated by the pointer, is directed along the line on the skin.

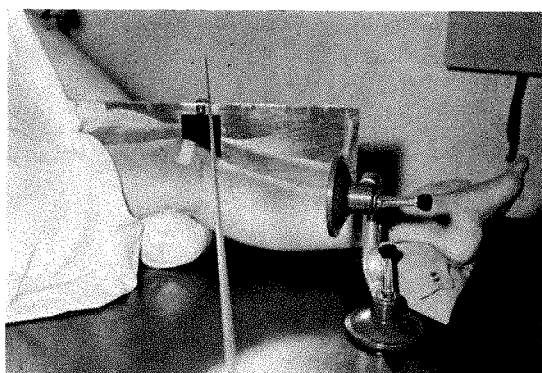


FIG. 5. Sixth exposure of the medial meniscus. The patient, who has been rotated 30° between each exposure, is now in a supine-oblique position with the anterior portion of the meniscus uppermost.

oblique position (Fig. 7). Examination of the lateral meniscus closely parallels that of the medial. At the extremes of rotation anteriorly and posteriorly, some difficulty may be encountered aligning the central beam with the mark drawn on the skin, and we have found that the best projections are obtained with the central ray close to a right angle with the long axis of the lower extremity. The examination is completed by taking anteroposterior and lateral Bucky roentgenograms with a vertical roentgen-ray beam.

TECHNICAL FACTORS

Low kilovoltage technique is essential to obtain maximum contrast, and short exposure times are desirable. In most patients



FIG. 6. Initial exposure of the lateral meniscus with the posterior portion uppermost. The leg is supported by the wooden table but, otherwise, the examination is the same as that of the medial meniscus.

50 to 52 kv. and 20 mas. (300 ma. at 1/15 to 1/10 second) have been used. The target film distance is approximately 48 inches; this is the length of the central ray pointer. The roentgen-ray beam is carefully collimated to cover the 2.5 by 7 inch window in the film holder.

DISCUSSION OF TECHNIQUE

A number of factors is important in obtaining satisfactory arthrograms. The upper tibial articular surface is inclined downward from front to back. The angle of inclination varies slightly with each patient, and, therefore, fluoroscopy and a carefully drawn line on the skin following the margin of the tibial plateau are important.

In using the medial approach, air and contrast material were successfully injected in most cases with the needle inserted approximately 1 inch or less, except in obese patients, where deeper insertion was occasionally necessary. In approximately 3 per cent of the patients in this series, part of the contrast material was injected into the extra-articular areas, apparently because the needle had been inserted too deeply. This, however, did not appreciably interfere with the interpretation of the arthrogram. Complete extra-articular injection occurred very rarely and required a second injection. This can be done as soon as the injected contrast material has been absorbed, after approximately 1 hour.

With the use of glucamine diatrizoate



FIG. 7. Sixth exposure of the lateral meniscus with the anterior portion uppermost.

(renografin 60 per cent), the patients had little or no discomfort when extra-articular injections occurred. However, the extra-articular injection of diatrizoate sodium (50 per cent hypaque) resulted in considerable pain.⁸ For this reason, we prefer renografin 60 per cent and have used it exclusively in the past 2 years. There was no appreciable difference in the quality of the roentgenograms obtained with intra-articularly injected renografin 60 per cent or hypaque 50 per cent.

If fluid is present in the knee joint, as much as possible should be aspirated because excess synovial fluid will significantly dilute the contrast material. Since it is not possible to aspirate all the fluid present, in these cases somewhat larger quantities of opaque medium (up to 10 cc.) were used. If no fluid is present, it is desirable to use as little contrast substance as possible; 5 cc. of renografin 60 per cent is sufficient.

In most patients, the examination could be performed with the knee extended. In some patients, satisfactory studies have been obtained with the knee locked in as much as 25 degrees of flexion. The examination becomes technically more difficult if the knee is locked in marked flexion.

Filming is performed with deliberate speed but without undue haste, and roentgenograms are processed and inspected immediately. It is usually possible to repeat in one or more projections if a satisfactory tangential view has not been obtained, or if an apparent abnormality is to be verified by further studies. With increasing delay between the injection of contrast and filming, a haziness of the outline of the meniscus develops and it is best to perform a second examination at a later date if the first is deemed technically unsatisfactory. This happened only once in our series, when a questionable meniscus tear was demonstrated with absolute certainty on the repeat examination.

The patient is told that the gurgling sensation in his knee may persist for up to 36 hours and is discharged.

The film holder, wooden table and alumi-

num central ray pointer are convenient aids in expediting the examination but are not essential. Satisfactory examinations have been obtained by making each exposure on a separate film, supporting the leg on pillows or a wooden block, and aiming the central beam with the assistance of an extension cone. The film holder allows the 6 tangential exposures of each meniscus to be made on a single 7 by 17 inch film in orderly sequence with the posterior and anterior projections of the cartilage at opposite ends of the film (Fig. 8, *A* and *B*). Interpretation is thus simplified, since it is not necessary to sort 12 different films.

NORMAL ARTHROGRAMS

Some knowledge of the normal anatomic relationships of the menisci is necessary for interpretation of arthrograms.

MEDIAL MENISCUS

The medial meniscus is a crescentic cartilage, triangular in cross section. Its outer surface is firmly attached to the medial collateral ligament. The superior and inferior surfaces lie free within the joint against the corresponding articular surfaces of the femoral and tibial condyles. Thus, in tangential view, the normal medial meniscus presents as a sharply defined wedge, its free inner margins thinly coated by positive contrast material and partially or completely enveloped by air (Fig. 9*A*). The base of the wedge is not outlined by contrast medium because of its attachment to the medial collateral ligament. Normally, no contrast substance will be present within the wedge or at its outer margin, except for a small contrast-filled synovial recess which is frequently seen below the antero-inferior margin of the medial meniscus (Fig. 9*B*), and a somewhat similar small synovial recess or fold posteriorly at the superior outer margin of the meniscus.

LATERAL MENISCUS

The lateral meniscus is more circular than the medial, but in cross section it is also triangular (Fig. 10, *A* and *B*). Thus, in

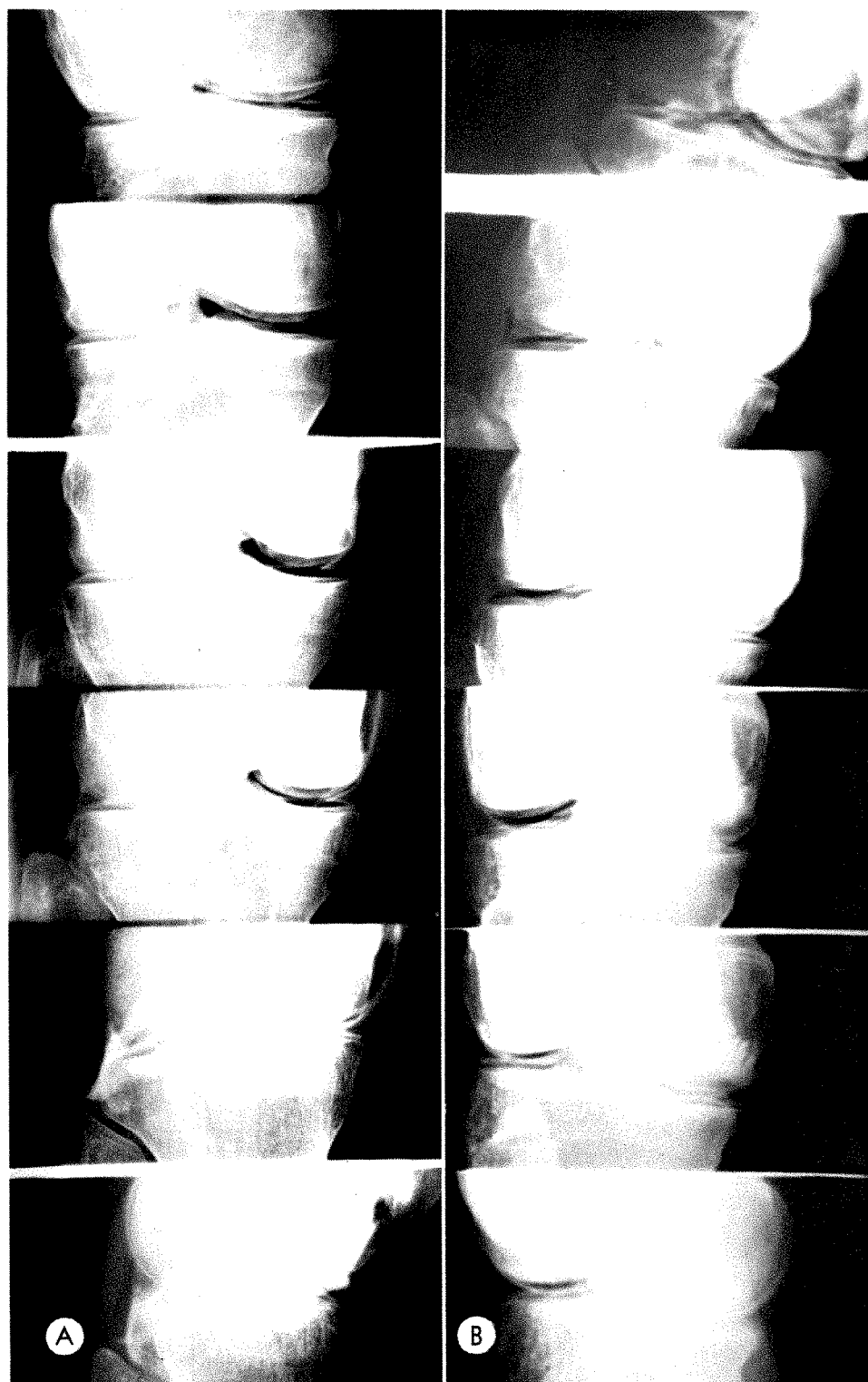


FIG. 8. (*A* and *B*) Normal arthrograms. The 6 tangential views of the medial meniscus are shown in *A* in orderly sequence on a single 7×17 inch film with the posterior portion at the top and the anterior portion at the bottom. Similarly, the lateral meniscus is shown in *B*.

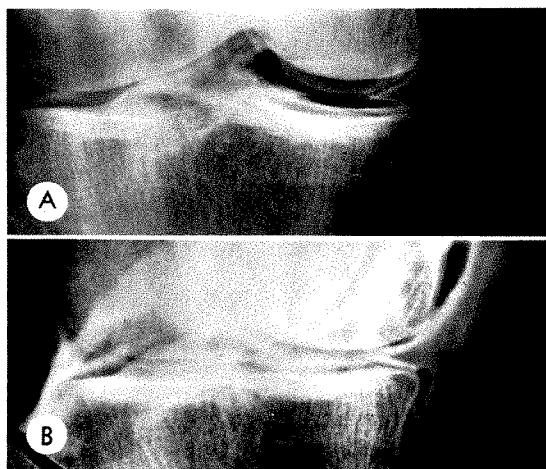


FIG. 9. (*A* and *B*) Detail views of the normal medial meniscus (4th and 5th exposures from *A* in Figure 8). In cross section the normal meniscus is a sharply defined wedge ($\leftarrow$). A small synovial recess ($\uparrow$) is frequently seen below the antero-inferior margin of the meniscus.

the normal arthrogram, it is similar in contour to the medial meniscus—a sharp wedge, its free inner margins thinly coated with positive contrast and enveloped by air. However, there is a significant difference between the lateral and the medial meniscus in the manner of attachment to their peripheral ligaments. Anteriorly and laterally, no contrast material will be seen at the base of the wedge, since here the lateral meniscus is attached to the lateral ligament. Posteriorly, it is separated from the ligament by the sleeve of the popliteus tendon which obliquely crosses the outer surface of the meniscus. Since the sleeve communicates with the joint, it fills with air and opaque material which will be seen at the base of the wedge posteriorly, giving the meniscus a partially detached appearance (Fig. 10*A*). A contrast-filled synovial recess is commonly seen anteriorly between the inferior portion of the base of the wedge and the lateral ligament. The margins of these normal contrast-filled structures are smooth and conform to a known pattern, thus differentiating them from tears; nevertheless, they make evaluation of the lateral meniscus more difficult than that of the medial.

Occasionally, the gastrocnemius semimembranosus bursa¹⁷ fills with contrast medium and, when it is large (a so-called popliteal cyst), it may interfere with evaluation of the posterior portion of the medial meniscus.

ABNORMAL ARTHROGRAMS

Tears present as abnormal collections of contrast substance within the wedge-shaped cross-sectional view of the meniscus and/or as a deformity in the contour of the wedge. Brief consideration of the basic types of tears is helpful in understanding the abnormal arthrogram (Fig. 11).

VERTICAL CONCENTRIC TEAR

When fragments remain in close apposition, a vertical line of opaque material will be seen within the wedge (Fig. 12*A*). When fragments are separated moderately, air and opaque medium will bisect the meniscus (Fig. 12*B*). When the inner fragment is displaced into the center of the joint, it usually cannot be seen on the arthrogram,

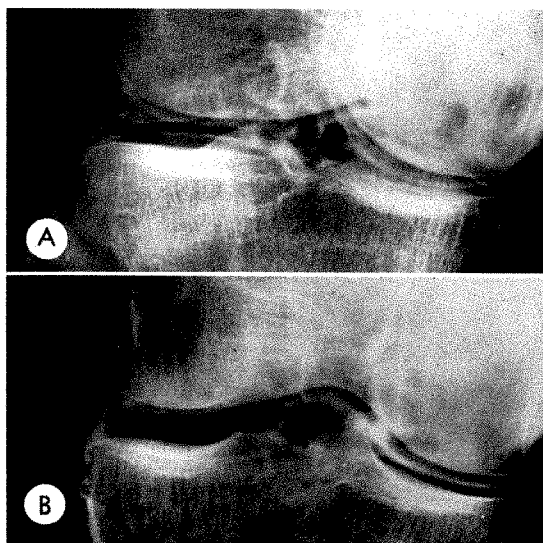


FIG. 10. (*A* and *B*) Detail views of the normal lateral meniscus (2nd and 3rd exposures from *B* in Figure 8). In cross section the lateral meniscus is also a sharply defined wedge. Posteriorly (*A*), it is separated from the lateral ligaments by the popliteus tendon ($\rightarrow$) which fills with air and opaque medium. This structure makes the interpretation of the lateral meniscus more difficult than that of the medial.

but the residual outer fragment will be abnormally narrow and blunt (Fig. 12C).

VERTICAL RADIAL TEAR

The arthrographic finding may be subtle, the only abnormality being a relative increase in density of the inner portion of the wedge, representing a layer of contrast material within the tear which is perpendicular to the roentgen-ray beam. Usually, the area of increased density has a relatively sharply defined outer margin, so that the difference in density is easily identified. An example of a radial tear is shown in Figure 12I, in which a diamond-shaped density is seen in the inner two-thirds of the wedge, and in Figure 12D where a more obvious triangular area of increased density is superimposed upon the major portion of the wedge. In a shallow tear, a small collection of opaque material will obscure the apex of the wedge, as shown in Figure 12E.

HORIZONTAL TEAR

A horizontal or oblique tear is easily recognized as a line of opaque material extending outward into the wedge from either the upper or under surface of the meniscus (Fig. 12F).

COMBINED FORMS

Frequently, the tear is a combination of these basic configurations. An example is shown in Figure 12G; the apex of the wedge is partially obscured by a collection of contrast material as in a radial tear, and a line of contrast medium extends outward as in a horizontal tear. In some cases the meniscus contains multiple tears, producing gross deformity of contour and multiple collections of opaque material within the deformed wedge.

Since tears are usually a complex combination of the basic types, in practice no attempt is made to classify the tear; however, we do indicate its location by determining on which projections it is shown. In many cases the tear is extensive and the abnormal findings will be present in several views. The localization of the tear is often helpful to the surgeon, particularly when it

BASIC TYPES OF MENISCAL TEARS

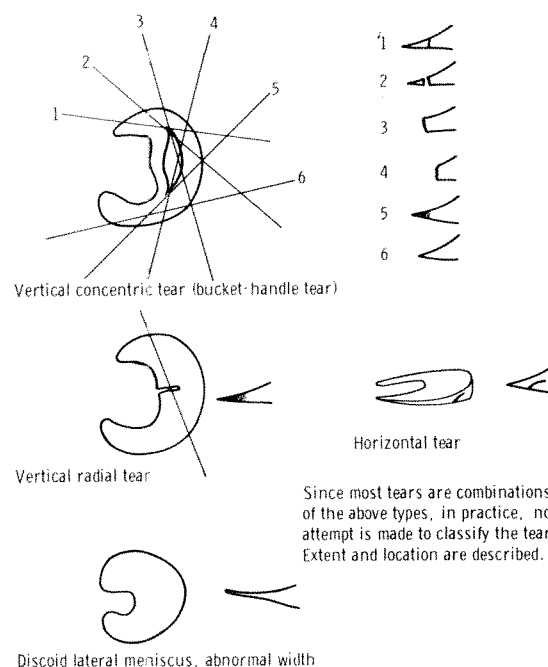


FIG. 11. The numbered lines through the diagram of the bucket-handle tear represent the roentgen-ray beam in the 6 tangential views obtained. The cross sectional views of the meniscus, as seen on the arthrogram, are illustrated on the right.

is in the posterior portion of the meniscus, since this area is difficult to examine through the commonly employed anterior approach.

DISCOID LATERAL MENISCUS

The discoid meniscus presents as an abnormally wide wedge with a thin inward extension toward the center of the joint (Fig. 12H). A torn discoid meniscus presents configurations similar to those described above. A radial tear in a discoid lateral meniscus is shown in Figure 12I. The abnormal width of the cartilage is more obvious in Figure 12H, a more posterior projection in which the tear is less clearly visible. Figure 12J demonstrates an irregular vertical concentric tear of a discoid meniscus in which the thin inner portion is separated from the body of the cartilage by air and opaque medium.

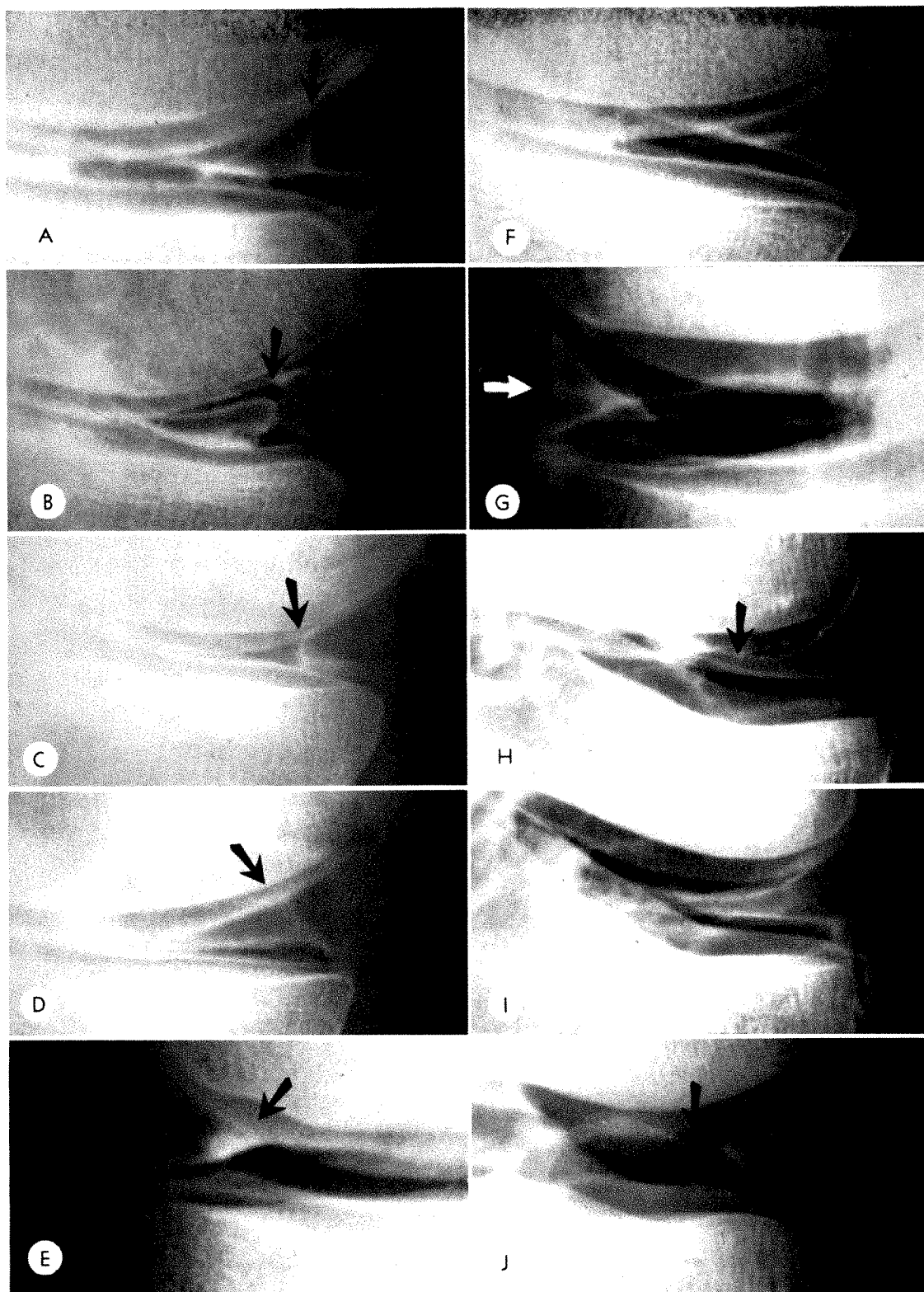


FIG. 12. Abnormal arthrograms. (*A*, *B* and *C*) Examples of vertical concentric tears in medial menisci. (*D* and *E*) Vertical radial tears in medial menisci. (*F*) Horizontal or oblique tear in a medial meniscus. (*G*) Combination of radial and horizontal tears in a medial meniscus. (*H* and *I*) Discoid lateral meniscus. A radial tear is shown in the more anterior portion of the meniscus (*I*). (*J*) Vertical concentric tear in a discoid lateral meniscus.

CYSTS OF THE MENISCUS

The clinical diagnosis of a cyst of the lateral meniscus could not always be substantiated by the arthrogram because the cysts encountered were located on the lateral margin of the meniscus and did not sufficiently distort its intra-articular portion. Cysts of the meniscus do not communicate with the joint and thus will not be opacified. Only cysts within the intra-articular portion of the meniscus sufficiently large to distort its contour can be diagnosed.

TEAR OF THE COLLATERAL LIGAMENT

A surgically verified diagnosis of tear of the medial collateral ligament was made in 2 patients by observing a distinctive line of opaque medium in the region of the ligament. This occurs when the traumatic rupture is sufficient to disrupt the joint capsule so that contrast medium leaks from the joint into the tissue plane adjacent to the ligament.

ARTHROGRAMS IN DEGENERATIVE ARTHRITIS

Several patients with degenerative arthritis had arthrography performed because clinical findings also suggested a meniscal tear. In some, the arthrograms were accurately interpreted without difficulty. Either an obvious tear was seen or less commonly, no abnormality of the meniscus was present. In other patients, a perplexing finding was minor irregularity of contour at the apex of the wedge, not sufficient to be considered a definite tear but the appearance of the meniscus was not completely normal. This was interpreted as "degenerative change without major tear" and in the 2 patients explored, the arthrographic findings were confirmed. The excised specimens were friable with slightly irregular margin but no real tears were present.

POSTOPERATIVE ARTHROGRAMS

Arthrography in patients who have had previous meniscectomy did not provide reliable information regarding the adequacy of previous excision. Regrowth of

fibrocartilage and fibrous tissue presented as a wedge somewhat similar in appearance to the normal meniscus, but usually blunt and narrow. In many cases, this wedge of fibrous tissue or fibrocartilage was sufficiently wide to suggest that a sizable remnant of cartilage had been left in the knee; however, at the second exploration, little or no true cartilage could be found in some of these cases. In patients having had previous medial meniscectomy, arthrography could be useful in evaluation of the lateral meniscus, or vice versa.

EVALUATION OF ACCURACY

All arthrograms made by us using the double contrast method with horizontal roentgen-ray beam are included in this evaluation. Despite our initial inexperience with the technical procedure as well as film interpretation, diagnosis with regard to lesions of the menisci was accurate in 103 of 113 cases (91 per cent), (excluding patients with previous meniscectomy). The evaluation of the small number of arthrograms following meniscectomy was not reliable with regard to the adequacy of previous excision or recurring tear, the diagnosis being correct in only 8 of 13 cases. Correct diagnoses and the errors which were made are shown in Table 1.

In reviewing the arthrograms in which our interpretation was at variance with findings at operation,* we found in a few cases that the arthrograms were technically imperfect. However, there were a few tears confirmed at surgery which were not visible on technically excellent arthrograms. This study was limited to the evaluation of the menisci, and no attempt was made to demonstrate ruptures of the cruciate ligaments or to define loose bodies within the knee.

COMPLICATIONS AND INVESTIGATION
OF EFFECTS OF ARTHROGRAPHY

No clinically significant complications were encountered in this series comprising 326 knee arthrographies. A single minor complication was the occurrence of mild urticaria arising approximately 10 minutes after the injection of the knee joint. Follow-

TABLE I

Statistics	
Total no. of knee arthrographies.....	324
No. explored surgically.....	126
No previous surgery.....	113
Correct.....	103 (91%)
Both menisci normal.....	26
Tear of medial meniscus.....	58
Tear of lateral meniscus.....	10
Tear of both menisci.....	2
Discoid lateral meniscus.....	4
Discoid lateral meniscus, tear of medial meniscus.....	1
Degenerative arthritis, no major meniscal tear.....	2
Incorrect.....	10 (9%)
Reported normal, tear found.....	4
Reported torn, found nor- mal.....	3
One meniscus reported torn, both found torn.....	1
Both menisci reported torn, one found torn.....	1
Borderline findings, prob- able tear reported, no tear found.....	1
With previous surgery.....	13
Correct.....	8 (61%)
Incorrect.....	5 (39%)

ing administration of chlortrimeton, the urticaria subsided during a 2 hour period of observation in the X-Ray Department. This complication was not unexpected, since similar allergic reactions do occasionally occur with intravenous urography using the same agent. As with intravenous urography, an emergency kit is always in the examining room.

The surgeons performing the arthrotomies were questioned as to any unusual appearance of the synovia. None was grossly evident on arthrotomy performed at intervals ranging from a few hours to weeks and months after arthrography. In most cases, surgery was performed 1 to 2 days after arthrography, and in these instances the synovial fluid often had a foamy appearance, apparently resulting from a mixture of the injected air and synovial fluid.

During the past year we requested the surgeons to perform synovial biopsies. Because this is not a routine procedure during meniscectomy, this request was frequently forgotten, and for this reason only 21 synovial biopsies were obtained in unselected patients. The time interval between arthrography and synovial biopsy ranged from 1 day to 3 months (Table II). Histologic examination of the biopsied synovia did not reveal any unusual findings which could be attributed to the arthrography. A few cases of chronic inflammatory changes consistent with long-standing internal derangement were present. In 1 case, a patient who had previously had an excision of the medial meniscus but continued to have knee pain had a second exploratory operation, and a tentative histologic diagnosis of rheumatoid arthritis was made.

SUMMARY

Double contrast arthrography using a horizontal roentgen-ray beam was performed on 326 patients with only 1 minor and transient complication.* The procedure, which is described in detail, is simple

TABLE II
SYNOVIAL BIOPSY
POST ARTHROGRAPHY

Time Post Arthrography	No.
1 day	5
2 days	2
3 days	1
4 days	1
5 days	1
7 days	1
13 days	1
14 days	1
1 month	3
1½ months	2
2 months	2
3 months	1
Total	21

* A total of over 600 knee arthrographies has been performed up to May, 1966. The accuracy of interpretation was 90 per cent. Complications: 2 cases of mild urticaria.

and does not interfere with the patient's activities.

The normal and the abnormal meniscus is described and illustrated.

With regard to lesions of the menisci, the roentgenographic diagnosis was confirmed in 91 per cent of the 113 patients explored who had not had previous meniscectomy. Arthrography in the postoperative knee did not provide reliable information as to the adequacy of previous meniscectomy.

Tear of the meniscus is a very common lesion. While the accuracy of clinical diagnosis is relatively high, the physical findings are atypical in a significant number of patients. In this group, arthrography is of particular value and should be more widely employed.

Robert H. Freiburger, M.D.
Hospital for Special Surgery
535 East 70th Street
New York, New York 10021

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COMPARATIVE MAMMOGRAPHY STUDY*

By JAMES V. ROGERS, JR., M.D.,[†] R. WALDO POWELL, M.D.,[‡] and
R. L. EGAN, M.D.[†]
ATLANTA, GEORGIA

IN 1959, two of the authors (JVR and RWP) began a concerted effort to use mammography in the diagnosis of breast diseases at Emory University Hospital. Using techniques advocated at that time, the quality of the studies was such that only 50 per cent of the breast cancers could be diagnosed from roentgenograms. After the introduction of a low kv., high mas. technique, used with a slow industrial film (Egan,² 1960), the quality of the studies improved dramatically and the number of cancers detected increased to 88 per cent.^{4,5} With this experience, the authors undertook a comparative study in mammography based on cases at Emory University Hospital beginning July 1, 1963, and extending through June 30, 1965. The dual purpose of this study was:

1. To train approximately 50 radiologists and their technicians from the Southeastern area in the technique for mammography devised by Egan.
2. To obtain additional data on the value of mammography in approximately 3,000 patients with breast symptoms so that one might gain a more complete understanding of: (a) the relative accuracy of clinical and roentgenographic examination in breast diseases; (b) the influence of clinical information on roentgenographic interpretation; (c) the effect of varying degrees of experience on the accuracy of interpretation of mammograms by qualified radiologists; (d) the effect of variations in technical quality with the Egan technique on the accuracy of interpretation; (e) the influence of the patient's age on the accuracy of diagnosis of breast cancer; (f) the im-

portance of the stage of disease in the diagnosis of breast malignancies; and (g) the incidence of clinically unsuspected breast cancer in this selected group of patients.

MATERIALS AND METHODS

It was anticipated that about 1,600 patients would be studied at Emory University Hospital by mammography in the 2 year period. In order to obtain a comparable series of patients from other hospitals, invitations were extended to radiologists and technicians from 19 institutions to participate in a cross reading program. Seventeen teams accepted this offer and spent a minimum of 3 days at Emory University Hospital studying mammographic technique and interpretation.* Each radiologist agreed to submit mammograms on 100 consecutive patients for cross reading and to forward pathology reports on those patients having subsequent breast biopsies. One or two of these teams were instructed each week in the first months of the program.

All patients referred for mammography

* (1) University of Ala. Med. Center, Birmingham, Ala., Felix Henley, M.D.; (2) Mobile Infirm., Mobile, Ala., John D. Peake, M.D.; (3) St. Margaret's Hosp., Montgomery, Ala., William F. Little, M.D.; (4) Tallahassee Memorial Hosp., Tallahassee, Fla., W. F. Lindsey, M.D.; (5) Med. Col. of Ga., Augusta, Ga., James Crawley, M.D., Mark Brown, M.D.; (6) Louisville Gen. Hosp., Louisville, Ky., Raul Gonzalez, M.D.; (7) Holy Cross Hosp. of Silver Spring, Maryland, Ed. D. Soma, M.D.; (8) Charlotte Memorial Hosp., Charlotte, N. C., D. Reed Tickle, M.D.; (9) N. C. Baptist Hosp., Winston-Salem, N. C., L. B. Leinback, M.D.; (10) Med. College Hosp., Charleston, S. C., S. E. Puckette, M.D.; (11) Columbia Hosp., Columbia, S. C., George W. Smith, M.D.; (12) Gen. Hosp., Greenville, S. C., Sam H. Fisher, M.D.; (13) E. Tenn. Baptist Hosp., Knoxville, Tenn., Wm. A. Nelson, M.D.; (14) Baptist Memorial Hosp., Memphis, Tenn., James L. Booth, M.D.; (15) Vanderbilt Univ. Hosp., Nashville, Tenn., Wm. Hill, M.D.; (16) Med. College of Va., Hosp., Richmond, Va., Gerald A. Gildersleeve, M.D.; (17) W. Va. Med. Center, Morgantown, W. Va., Joseph A. Chang, M.D.

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From the Departments of Radiology and Surgery, Emory University School of Medicine, Atlanta, Georgia.

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[†] Associate Professor of Radiology, Emory University.

[‡] Associate Professor of Surgery, Emory University.

were to have appropriate data submitted by their physician including (1) a tentative diagnosis of no disease, benign disease, indeterminate (suspicious of cancer), or cancer, (2) the indication for mammography, and (3) the location of abnormal findings within the breast.

In order to obtain data regarding the influence of clinical information and the experience of the radiologist on mammographic interpretation, cross readings were performed in the following manner:

1. Mammograms from participating institutions: (a) The radiologist from a participating institution (designated as Radiologist I) who had minimal experience in mammography interpreted his own studies with full knowledge of clinical findings; (b) JVR (Radiologist II) with moderate experience in mammography interpreted the same mammograms with no clinical information; and (c) RLE (Radiologist III) with extensive experience in mammography interpreted the same mammograms with no clinical information.

2. Mammograms from Emory University Hospital: (a) JVR interpreted these studies with full knowledge of clinical findings; and (b) RLE interpreted the same studies with no clinical information.

RESULTS

Table I lists the total number of patients and breasts studied. One out of 5 (20 per

cent) of the breasts roentgenographed were biopsied and one-third of these proved to have cancer. One out of 3 patients in the study underwent biopsy, 117 patients had bilateral biopsy. Patients having had a previous mastectomy comprised 13 per cent of the population (7 per cent of the breasts roentgenographed), and male patients another 1 per cent.

Table II lists the indications for mammography and shows the order of yield of cancer for each indication. The numerical order of frequency of occurrence of breast cancer for each indication was determined by dividing the percentage of malignancies by the percentage of breasts studied for each indication. Clinically suspected carcinoma produced by far the highest yield.

Table III indicates the accuracy for each examiner in the recognition of benign lesions. Any biopsy proven benign disease coded as cancer or suspicious of cancer was counted as an error (overcall). The clinician had a greater tendency to overcall than the radiologists. As experience in mammographic interpretation increased, there was a decrease in overcalls. Clinical information did not influence the overcall rate significantly (Radiologist II, 16 per cent overcall without clinical information *vs.* 14 per cent overcall with clinical information).

Table IV indicates the accuracy for each examiner in the recognition of cancer. Any proven case coded as no disease or benign

TABLE I

DISTRIBUTION OF COMPARATIVE MAMMOGRAPHY STUDY PATIENTS BY NUMBER OF BREASTS, SPECIFIED TYPE OF PATIENT AND DIAGNOSIS

Emory University Hospital, July 1, 1963—June 30, 1965

	16* Other Institutions	Emory University Hospital	Total	Per Cent of Breasts
Total patients	1,764	1,615	3,379	
Breasts studied	3,241	3,070	6,311	100
Previous mastectomy	287	160	447	7
Males	13	21	34	1
Biopsies	735	535	1,270	20
Benign biopsies	488	371	859	14
Malignancies	247	164	411	7

* One of the original 17 participating institutions failed to submit usable data.

TABLE II

CLINICAL INDICATION FOR MAMMOGRAPHY CORRELATED WITH CANCER YIELD

Indication for Mammography (as listed on clinical referral form)	Per Cent Indication (6,311 breasts)	Per Cent Occurrence (411 malignancies)	Order of Yield of Cancer
Carcinoma	6	62	1
Axillary lymphadenopathy or metastatic lesion	1	1	2
Dominant mass probably not carcinoma	23	17	3
Previous mastectomy for cancer	7	5	4
More than one breast mass	8	3	5
Breast complaint, no mass	9	3	6
Others, or not indicated (usually opposite breast from symptoms)	37	9	7
Extremely large breasts	2	<1	
Strong family history of mammary cancer	1	<1	
Previously proven fibrocystic disease	6	<1	

was counted an error (undercall). The radiologists with clinical information had the least number of undercalls. The "suspicious of cancer" category was used more when clinical information was available.

Table v shows that over-all accuracy varied little between clinicians, inexperienced and experienced radiologists. Since 80 per cent of the 6,311 breasts studied were not biopsied, the error rate for each examiner was diluted. When only the biopsy proven cases were considered, including both benign and malignant lesions, the

more experienced radiologists showed a lower percentage of error than the less experienced radiologists or the clinician. However, when only cancers were considered, clinical information was responsible for a lower error rate than experience in mammography.

Table vi shows the accuracy of cancer recognition by each examiner related to the age of the patient and the stage of disease. For this classification, Stage 0 is carcinoma *in situ* (6 cases), Stage I is noninflammatory carcinoma confined to the breast without extensive local disease (90 cases), Stage II is carcinoma with axillary lymph node involvement with or without extensive local disease (55 cases), and Stage III is carcinoma with distant metastases, usually with extensive local disease (13 cases). The accuracy of cancer detection was influenced by both the patient's age and the stage of the disease. Clinical information had little influence on the accuracy of mammographic interpretation in Stages II and III, but a pronounced effect was noted in Stages 0 and I.

Table vii shows that 5 per cent (21 cases) of all breast cancers were not suspected clinically. Fourteen of the 21 cases were coded as no disease clinically and no lesion could be palpated on repeat examination. In the remaining 7 cases, there were no clinical findings in the breast to suggest

TABLE III

COMPARATIVE ACCURACY IN DIAGNOSIS
OF BENIGN LESIONS

	Other		Emory University Hospital	
	Benign or No Disease	Per Cent	Benign or No Disease	Per Cent
Pathology Dx.	488	100	371	100
Clinical Dx.	291	60	304	82
Radiol. I	374	76*		
Radiol. II	409	84	310	86*
Radiol. III	444	91	358	96
No. of Studies				
Coded Poor**	149	31	8	2

* With clinical information.

** Mammogram considered poor by one or more radiologists.

TABLE IV
COMPARATIVE ACCURACY IN DIAGNOSIS OF MALIGNANCIES

	Other			Emory University Hospital		
	Cancer	Suspicious of Cancer	Per Cent	Cancer	Suspicious of Cancer	Per Cent
Pathology Dx.	247		100	164		100
Clinical Dx.	168	49	88	112	32	88
Radiol. I	184	30	88*			
Radiol. II	174	23	80	110	27	84*
Radiol. III	191	2	78	115	0	70
No. of Studies Coded Poor**	94		38	7		4

* With clinical information.

** Mammogram considered poor by one or more radiologists.

cancer on physical examination, although there was some complaint or finding referable to the breast. In 12 per cent of the cancers, none of the radiologists suggested the correct diagnosis. Review of 25 cases from Emory University Hospital incorrectly coded by both radiologists showed no significant pathologic changes in 15 cases. In 10 cases, equivocal changes were present on the mammograms which may have been suggestive enough to require biopsy even though coded benign.

Eleven, or 3 per cent, of the cancer patients had bilateral simultaneous primary lesions. Three additional patients had bilateral cancer but with metastasis to the second breast; these latter were inflamma-

tory cancer. Five per cent of the cancers were in patients who had had previous mastectomy for cancer.

DISCUSSION

Comparison of the over-all clinical accuracy shows 97 per cent at Emory University Hospital as compared to 93 per cent at other participating institutions (Table v). Table III shows that the reason for this difference was a considerably higher overcall rate by the participating clinician because of a more generous usage of the "suspicious of cancer" category. The great majority of the breast biopsies were for the purpose of either proving or excluding cancer, so in a sense nearly all of the benign biopsy proven

TABLE V
RELATIONSHIP OF RADIOLOGIC INTERPRETATION TO CLINICAL INFORMATION AND EXPERIENCE

	Over-All Accuracy		Accuracy in Biopsy Proven Breasts		Accuracy in Malignancies	
	Other	Emory University Hospital	Other	Emory University Hospital	Other	Emory University Hospital
	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent
Clinical	93	97	70	84	88	88
Radiol. I	96*	—	80*	—	88*	—
Radiol. II	96	97*	83	85*	80	84*
Radiol. III	97	98	88	88	78	70

* With clinical information.

TABLE VI

DIAGNOSTIC ACCURACY IN BREAST CANCER RELATED TO STAGE OF DISEASE AND AGE OF PATIENT—
EMORY UNIVERSITY HOSPITAL ONLY

Age	Stage	Total	Per Cent	Interpreted Malignant					
				Clinical		Radiol. II*		Radiol. III	
				No.	Per Cent	No.	Per Cent	No.	Per Cent
Under 50 Yr.	O and I II and III	41	25	29	71	25	61	13	32
		26	16	24	93	22	85	22	85
Over 50 Yr.	O and I II and III	55	34	50	91	49	89	40	73
		42	25	41	98	41	98	40	95

* With clinical information.

97 over 50
67 under 50

96 Stage O and I
68 Stage II and III

cases were overcalls regardless of how they were coded by the clinician. The clinical accuracy in detecting cancer was 88 per cent. Of the remainder, 7 per cent were discovered because of a dominant clinical finding, coded benign but suspicious enough to warrant biopsy, and 5 per cent because of suspicious or positive mammographic findings.

The accuracy of cancer detection by the radiologists was better in the group of patients from participating institutions than from Emory University Hospital. This is explained by the age of the patients and the stage of the disease. Whereas 41 per cent of the Emory University Hospital cancer patients were under 50 with an average age of 54.2 years, only 28 per cent of the cancer

patients from other institutions were under 50 with an average age of 56.8 years. Since the demonstration roentgenographically of a breast mass depends in part on the amount of fat present to furnish contrast, it follows that younger women with less fatty deposition and more fibroglandular tissue will pose more difficult problems. This has already been demonstrated in other studies.¹ The age of 50 years was chosen as an arbitrary dividing point since most women over 50 have considerable fatty deposition in the breast. Actually, there is a gradual increase in the amount of fatty deposition from postpuberty to postmenopausal years. It is of interest that the firmer breast of the younger patient led to greater clinical as well as roentgenographic

TABLE VII

DATA ON MALIGNANCIES

	Other	Emory University Hospital	Total	Per Cent of Total
Total malignancies	247	164	411	100
Clinically unsuspected (6 in remaining breast)	12	9	21	5
Coded benign by all radiologists	23	25	48	12
No mass or secondary signs on mammography	unknown	15	15/164	9
Malignancies in remaining breast	10	13	23	5
Simultaneous bilateral primaries (no. of patients)	5	6	11	3
Malignancies in males	1	0	1	0.2

inaccuracy. It was apparent that the cancers from the participating institutions were, in general, more advanced, although our data did not permit us to stage many of these patients.

The discrepancy in detection of Stage 0 and I cancer by Radiologist II and III at Emory University Hospital is explained by the availability of clinical findings to Radiologist II. Nearly all Emory University Hospital patients were examined by one of the authors (RWP) with considerable experience in breast disease as well as by one or more referring physicians. Usually he (RWP) and Radiologist II reviewed the mammograms together prior to interpretation. Radiologist II made significantly more overcalls than Radiologist III, suggesting that the inverse ratio of overcalls to undercalls may also be exerting an influence.

A more realistic comparative evaluation is the productivity of cancer diagnosis: 3.5 biopsies based on clinical findings produced 1 cancer, while 1.4 biopsies based on mammographic findings yielded 1 cancer.

If one attempts to compare the clinically unsuspected and roentgenographically unsuspected cancers (Table VII), it is more logical to use 9 per cent as the figure for roentgenographically unsuspected cancer, since a number of patients coded benign on mammography had roentgenographic findings which could justify biopsy. Any dominant mass not unquestionably benign, or any localized cluster of small irregular calcifications noted on mammography deserves further investigation at the present state of our knowledge of breast diseases. On this basis, 58 biopsies were performed because of mammographic findings to yield the 21 unsuspected cancers. This ratio of 1 cancer to 2 benign lesions is the same as the biopsy ratio for clinically indicated biopsies in the larger group of patients. Nearly one-third of these clinically unsuspected cancers were in the remaining breast after previous mastectomy for cancer. Indeed, if one totals the number of cancers occurring in the remaining breast with the number with bilateral simultaneous involvement in this

study, it is nearly 10 per cent of the patients with cancer. This points out the importance of great attention to the opposite breast in a patient with known cancer of one breast.³

From Tables III and IV, it can be seen that about 35 per cent of the mammograms from participating institutions were coded as poor by one or more radiologists as compared with about 3 per cent from Emory University Hospital. However, this did not seem to have a significant influence on the accuracy of interpretation. In only 2 or 3 cases were the studies considered unsatisfactory for interpretation in which case they were counted as misses. This latitude with the Egan technique does not hold for other techniques using faster film in our experience.

SUMMARY AND CONCLUSIONS

Based on a 2 year program in mammography in which comparisons were made between results on patients studied at Emory University Hospital and 16 participating institutions, the following conclusions seem justified:

1. Both radiologists and technicians can be trained to do competent mammography in a brief period of time.
2. There is a wide latitude in roentgenograms of diagnostic quality using the Egan technique for mammography.
3. For the best results in breast cancer detection, both clinical examination and mammography should be combined. Although the accuracy by either method is only 88 per cent, each potentiates the other so that cancers overlooked by one examination are likely to be recognized by the other. Thus, it is obvious that neither a negative mammogram nor a negative clinical examination excludes breast cancer.
4. There is a definite improvement in cancer detection by mammography if clinical information is used.
5. Cancer can be detected with relative ease in the older patient with fatty breasts as compared to the younger patient with dense fibroglandular breasts. This is espe-

cially true of mammography, although it applies clinically as well.

6. In general, the less advanced the cancer, the more difficult it is to detect both roentgenographically and clinically.

7. Five per cent of the breast cancers in this selected group were unsuspected clinically. Twelve per cent were not identified roentgenographically.

James V. Rogers, Jr., M.D.
Department of Radiology
Emory University School of Medicine
Atlanta, Georgia

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EXPERIMENTAL EVALUATION OF CONCENTRATED SOLUTIONS OF IOTHALAMIC ACID DERIVATIVES AS ANGIOGRAPHIC CONTRAST MEDIA*

By CAULEY W. HAYES, M.D., JOHN H. FOSTER, M.D., ROBERT SEWELL, B.S.,
and DUNCAN A. KILLEN, M.D.
NASHVILLE, TENNESSEE

AN EVER increasing utilization and application of contrast angiography dictates a continued search for newer and safer contrast media—especially for use in the coronary and cerebral circulation. Previous reports from this laboratory have documented the fact that angio-conray (sodium iothalamate 80 per cent) and hypaque M-90 per cent (2:1 mixture of N-methyl glucamine and sodium diatrizoate) are the least toxic of the currently available *concentrated* angiographic contrast media.^{1,2} Even so, in experimental animals each of these media have easily demonstrable neurotoxic and nephrotoxic effects.^{6,7} Recently, 2 new preparations of iothalamic acid derivation (MP 1005.2 and MP 2032) have been made available. These preparations contain exactly the same proportion of N-methyl glucamine and sodium salts (2:1) and same iodine content (461 mg./cc.) as does hypaque M-90 per cent. MP 1005.2 is an experimental formulation of iothalamate, whereas MP 2032 is a double ring derivative of iothalamate (Fig. 1). These agents have been tested and evaluated as to their toxicity and efficiency when used as an angiographic contrast medium and results have been compared to the results of the same tests with hypaque M-90.

MATERIALS AND METHODS

Standardized methods of testing animal tolerance to intra-aortic, intravenous and renal arterial administration of angiographic contrast media have been described previously and will be summarized briefly.^{7,8}

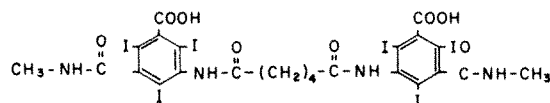


FIG. 1. Chemical formula of MP 2032.

REPEAT AORTIC INJECTION TEST

Healthy mongrel dogs were anesthetized with 30 mg. per kilogram of body weight of veterinary pentobarbital (nembutal) and, using sterile technique, the abdominal aorta was exposed at laparotomy. The tip of a No. 18 needle was then inserted into the aorta 1 cm. below the origin of the left renal artery and the needle slanted cephalad so that its tip lay at the level of the left renal artery. Fifteen cubic centimeters of the contrast medium was then injected manually into the aorta over a period of 5 to 10 seconds. Fifteen minutes later another identical injection of 15 cc. of the contrast medium was made. The laparotomy incision was then closed. The animals were observed for evidence of neurotoxicity which was measured first in terms of immediate response to the injection (hyperextension, hyperirritability or seizure in the hind limbs) and later in regard to evidence of post-anesthetic neurologic deficit. The nephrotoxicity of the agent was assessed by comparison of serial nonprotein nitrogen values to the preinjection control values and by histologic study of the kidneys. Surviving animals were sacrificed 1 week after the injection.

* From the S. R. Light Laboratory for Surgical Research, The Surgical Research Laboratory, Veterans Administration Hospital, and the Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee.
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INTRAVENOUS INJECTION TEST

In these dogs, under local anesthesia, a PE 240 catheter was inserted into the thoracic inferior vena cava via a femoral vein. The contrast medium was injected rapidly (12.5 cc. per second) in dosages from 3 to 7 cc. per kilogram of body weight. The animals were observed carefully for objective changes in neuromuscular activity, for changes in cardiopulmonary status and for the occurrence of rapid death.

RENAL ARTERIAL INJECTION TEST

Renal toxicity was assessed by the isolated infusion of the contrast medium into the renal arteries. Following induction of general anesthesia, the abdominal aorta was exposed by a midline laparotomy incision. The aortic segment from which the renal arteries arise was mobilized from all surrounding structures. A curved vascular clamp was placed across the aorta so that the aorta was transiently occluded above and below the origin of the renal arteries. A volume of 15 cc. of the test contrast solution was injected into the isolated aortic segment so that all the injected solution passed undiluted into the renal arterial bed. Following the injection, the vascular clamp was immediately removed, thereby re-establishing renal blood flow. The period of aortic occlusion was always less than 1 minute. The laparotomy incision was repaired by routine techniques. Serum nonprotein nitrogen determinations were performed preoperatively and on alternate days postoperatively until demise or sacrifice of the animal, at 1 week. A rise of the nonprotein nitrogen to a value greater than 50 mg. per cent was arbitrarily termed *azotemia*. Elevation of the nonprotein nitrogen to a value greater than 100 mg. per cent was arbitrarily termed *severe azotemia*. Renal specimens obtained at autopsy were fixed, mounted, and stained for histologic study. The histologic sections of each animal were reviewed and categorized as to the severity of renal tubular damage. *Minimal* changes included scattered areas of hy-

dropic degeneration of the tubular epithelium. *Moderate* changes consisted of scattered areas of tubular degeneration and/or necrosis associated with the accumulation of tubular proteinaceous casts. *Severe* changes consisted of massive tubular necrosis.

PHYSIOCHEMICAL STUDIES

The iodine content (mg./ml.) of each contrast agent was calculated. The viscosity of each of the contrast media was determined by a gravity flow pipette evacuation technique. Serial dilutions of the agents were prepared and the viscosity of each concentration was measured. The relative injectability of iodine for each of the prepared solutions was determined by calculation of the ratio of iodine content to viscosity.⁵

RESULTS

REPEAT AORTIC INJECTION TEST

Ten to 12 animals were used to test each of the contrast media. Tables I and II give the detailed results. With the two new agents, MP 1005.2 and MP 2032, there were no neurologic reactions (immediate or post anesthetic). There was no evidence of renal injury with MP 2032, while a single animal receiving MP 1005.2 sustained a rise in serum nonprotein nitrogen from a control level of 49 to 66 mg. per cent—the animal was azotemic at the time of sacrifice and histologic study revealed severe chronic interstitial nephritis but no evidence of tubular necrosis. This latter animal had a pre-existing azotemia. Table III gives results in comparable testing of hypaque M-90. With hypaque M-90 immediate neurologic reaction was observed in 8 of 10 animals and post-anesthetic deficit was found in 6 of 10 animals. There was no evidence of renal injury with hypaque M-90.

INTRAVENOUS INJECTION TEST

In the intravenous injection test, if an animal survives for 30 minutes it will usually survive indefinitely—a lethal re-

TABLE I
MP 1005.2 REPEAT INJECTION TEST

Dog No.	Weight (kg.)	Neurologic Response				Serum Blood Urea Nitrogen			
		Immediate Reaction	Post-Anesthetic Day			Control	2	Day 4	6
1. 276	12.4	o	o	o	o	15	16	15	14
2. 277	13.5	o	o	o	o	13	15	13	14
3. 278	11.5	o	o	o	o	16	13	15	14
4. 279	12.6	o	o	o	o	11	14	13	12
5. 785	13.0	o	o	o	o	18	20	16	18
6. 262	10.5	o	o	o	o	49	66	62	60
7. 690	14.4	o	o	o	o	17	32	16	19
8. 691	12.8	o	o	o	o	19	21	20	18
9. 707	12.0	o	o	o	o	19	31	16	17
10. 317	13.2	o	o	o	o	12	16	14	15
11. 319	14.0	o	o	o	o	17	18	18	17
Incidence of Response		o/11	o/10			1/11			

sponse is usually observed in 5 to 8 minutes. The mode of death is primarily pulmonary, manifest as acute pulmonary edema and thereafter by central nervous system symptoms (*i.e.*, convulsions, hyperirritability, defecation and urination). Injection of MP 2032 in dosages of 3 to 7 cc./kg. was completely free of mortality or untoward effect (Table IV). With MP 1005.2 a mortality of 20 per cent was encountered at the 4 cc./kg. dosage and this increased to the 60-70

per cent range with the 5, 6 and 7 cc./kg. dosages. With hypaque M-90 a 50 and 60 per cent mortality was encountered at the 3 and 4 cc./kg. dosage and any animal receiving more than 4 cc./kg. died. Figure 2 shows the results in graphic form.

RENAL ARTERIAL INJECTION TEST

Isolated renal artery infusion was performed as described in 38 animals. Two animals did not survive long enough (2

TABLE II
MP 2032 REPEAT INJECTION TEST

Dog No.	Weight (kg.)	Neurologic Response				Serum Blood Urea Nitrogen			
		Immediate Reaction	Post-Anesthetic Day			Control	2	Day 4	6
1. 270	13.0	o	o	o	o	21	14	11	11
2. 271	12.5	o	o	o	o	22	26	19	15
3. 272	11.8	o	o	o	o	20	30	18	18
4. 211	12.8	o	o	o	o	18	18	13	13
5. 28	11.0	o	o	o	o	17	22	17	16
6. 61	13.5	o	o	o	o	24	15	14	24
7. 94	12.0	o	o	o	o	19	15	13	16
8. 286	10.5	o	o	o	o	17	18	16	22
9. 451	11.8	o	o	o	o	18	17	15	14
10. 455	12.5	o	o	o	o	14	11	11	10
Incidence of Response		o/10	o/10			o/10			

TABLE III
HYPAQUE M-90 PER CENT REPEAT INJECTION TEST

Dog No.	Weight (kg.)	Neurologic Response				Serum Blood Urea Nitrogen			
		Immediate Reaction*	Post-Anesthetic Day			Control	Day		
			1	3	5		2	4	6
1. 410	13.5	+	ND	ND	ND	21	15	22	21
2. 424	10.5	++	P	HLP	HLP	15	21	13	16
3. 429	16.0	++	HLP	HLP	HLP	10	13	15	18
4. 436	12.0	+++	HLP	HLP	HLP	11	9	10	9
5. 443	12.5	o	ND	ND	ND	15	11	11	10
6. 459	17.1	++++	P	HLP	HLP	12	14	15	13
7. 460	11.2	o	ND	ND	ND	13	16	14	14
8. 471	12.0	+	HLP	HLP	HLP	15	12	16	14
9. 472	8.2	++	ND	ND	ND	13	10	9	9
10. 473	17.0	++	HLP	HLP	HLP	15	14	15	16
Incidence of Response		8/10	6/10			0/10			

* Immediate reaction consists of hyperextension, hyperirritability or seizure in the hind limbs.

ND—No deficit.

HLP—Hind limb paresis.

P—Paraplegia.

days) to permit post-injection evaluation of renal function. The cause of death could not be determined in these 2 animals. The post-injection renal function was evaluated in 36 animals and the results obtained are summarized in Table v. The incidence of azotemia was not significantly greater in any group of animals. The mean peak non-protein nitrogen was greater in the hypaque group than in either of the other test groups. There were no deaths in the group of animals receiving MP 1005.2. There were 3 deaths in the group of animals receiving MP 2032; however, in only 1 animal was the death associated with severe azotemia.

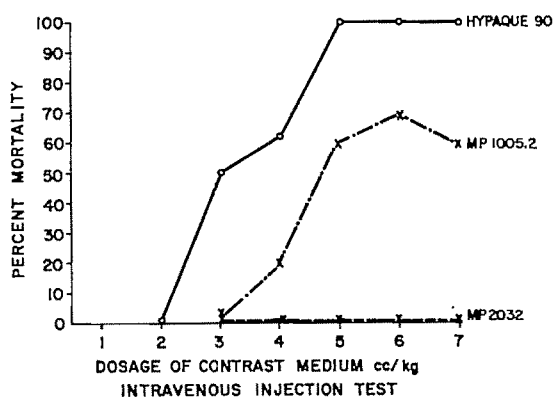


FIG. 2. Results of the Intravenous Injection Test with the 3 media.

TABLE IV
INTRAVENOUS INJECTION TEST (12.5 cc./sec.) INTO THORACIC INFERIOR VENA CAVA

Dosage cc./kg.	MP 1005.2		MP 2032		Hypaque M-90	
	Living	Dead	Living	Dead	Living	Dead
3	5	0	5	0	5	5 (50%)
4	8	2 (20%)	5	0	7	13 (65%)
5	4	6 (60%)	5	0	0	10 (100%)
6	3	7 (70%)	5	0	5	0 (100%)
7	4	6 (60%)	5	0	3	0 (100%)

TABLE V
RENAL FUNCTION FOLLOWING ISOLATED INFUSION OF THE RENAL ARTERIES

Contrast Agent	Animals	Azotemia (NPN—50 mg.%)	Severe Azotemia (NPN—100 mg.%)	Mean Peak NPN (mg.%)	Deaths
MP 1005.2	12	10	3	71	0
MP 2032	12	10	1	72	3*
Hypaque M-90	12	9	3	93	4

* Only 1 animal severely azotemic.
NPN—nonprotein nitrogen.

There were 4 deaths in the hypaque group, in each instance associated with azotemia. The histologic changes found in each group of animals are tabulated in Table VI. The severity of renal damage was greater in the hypaque group.

PHYSIOCHEMICAL STUDIES

The solution concentration, iodine content, and relative viscosity of the contrast agents are recorded in Table VII. It is noted that the roentgenographic characteristics of MP 1005.2 are superior to those of MP 2032 and hypaque M-90, *e.g.*, higher

TABLE VI
SEVERITY OF RENAL DAMAGE FOLLOWING
ISOLATED ARTERIAL INFUSION

Agent	No. of Animals		
	Minimal	Moderate	Severe
MP 1005.2	6	1	5
MP 2032	7	3	2
Hypaque M-90	2	4	6

TABLE VII
PHYSICAL AND ROENTGENOGRAPHIC
CHARACTERISTICS

Agent	Solution Concen- tration	Iodine Content (mg./ml.)	Relative Viscosity*
MP 1005.2	90%	462	1.8
MP 2032	92%	462	8.6
Hypaque M-90	90%	462	4.5

* Relative to water as unity at room temperature (26°C.).

iodine content and lower viscosity. Determination of the iodine injectability of various concentrations of the contrast media again confirms the superior roentgenographic properties of MP 1005.2 (Fig. 3).

DISCUSSION

The new concentrated angiographic contrast media (MP 2032 and MP 1005.2) which are derivatives of iothalamic acid have been submitted to animal tolerance tests and compared to results of similar tests with hypaque M-90. MP 1005.2 is a 2:1 mixture of N-methyl glucamine and sodium salts of iothalamic acid and thus the salt composition is the same as hypaque M-90. MP 2032 is a double ring compound similar to two molecular of iothalamic acid; it is the type of medium used for intravenous cholangiography—once again it was prepared as a 2:1 mixture of the N-methyl glucamine and sodium salts. The iodine content of MP 1005.2, MP 2032 and hypaque M-90 is exactly the same—462 mg. iodine/cc. This study thus compares equi-

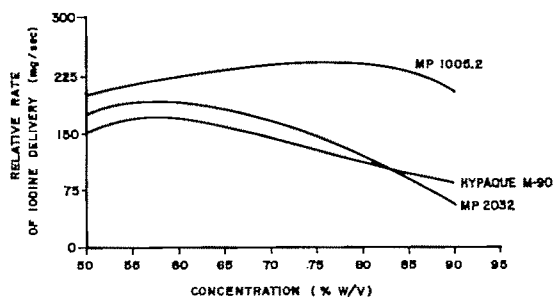


FIG. 3. The relative rates of iodine delivery with the 3 media in a simple gravity evacuation system.

valent solutions of diatrizoate salts (hypaque M-90) and iothalamate salts (MP 1005.2 and MP 2032).

In the Repeat Aortic Injection Test, both MP 2032 and MP 1005.2 were free of any significant neurotoxic or nephrotoxic effect, whereas, hypaque M-90 yielded a high incidence of neurotoxicity but no nephrotoxicity. The repeat Aortic Injection Test is the most severe test that we have used in testing abdominal aortographic contrast media.⁶ Ordinarily, the single Aortic Injection Test has been used in evaluating concentrated contrast media; with this test angio-conray and hypaque M-90 proved least toxic of all the currently available concentrated media.¹ The single Aortic Injection Test is in itself quite severe in that it employs a dosage twice that ordinarily used in clinical abdominal aortography.² The Repeat Aortic Injection Test provides an even more rigid trial—the 2 new compounds proved quite innocuous when utilized in this test.

In the Intravenous Injection Test, MP 2032 proved to be totally nontoxic even in 7 cc./kg. dosage. MP 1005.2 was considerably less toxic than hypaque M-90 when administered rapidly by the intravenous route.

In the Renal Arterial Injection Test, both MP 2032 and MP 1005.2 proved to be less nephrotoxic than hypaque M-90. It should be pointed out that this test provides the severest test that we have used for nephrotoxicity—roughly 0.5 cc. of contrast medium/kg. body weight into each renal artery.⁷ This is equivalent to the use of 35 cc. of a *concentrated* contrast medium to perform selective renal arteriography.

The physiochemical testing revealed that MP 2032 is of extremely high viscosity and the rate of iodine delivery per unit time in a standard system is very slow. These characteristics are even more unfavorable than with hypaque M-90. Usage of MP 2032 at this concentration thus seems impracticable—the extremely low toxicity of this agent in these studies may be, in part, due

to this high viscosity and coincident slow delivery rate. Nonetheless, it might prove valuable for peripheral arteriography at a lower concentration (*i.e.*, 300 mg. iodine/cc.) and proportionately lower viscosity. It *could* prove more suitable than conray (282 mg. iodine/cc.) or hypaque-50 (300 mg. iodine/cc.) for femoral, carotid or selective arteriography.

The viscosity of MP 1005.2 is quite favorable, far better than that of hypaque M-90. This medium may be quite satisfactory for abdominal aortography and, more importantly, superior to angio-conray for opacification of the ascending thoracic aorta where high concentrations may enter the coronary or cerebral circulation. We have been quite satisfied with the radiopacification of angio-conray in the ascending thoracic aorta but the occasional arrhythmia or grand mal seizure associated with its use in this location has forced us to cut back to a less concentrated medium for this examination.⁸ The lower toxicity of MP 1005.2 while maintaining a high radiopacification index (462 mg. iodine/cc. and relatively low viscosity) warrants evaluation of this medium in the thoracic aorta. There has been some evidence presented to indicate that the N-methyl glucamine salts of the contrast media are safer in the coronary circulation than the sodium salts—in this respect; if this be true, MP 1005.2 might also be safer than angio-conray.⁴

SUMMARY

Two new concentrated contrast agents, MP 1005.2 and MP 2032, which are derivatives of iothalamic acid have been tested as angiographic contrast media. The results have been compared to results obtained with hypaque M-90; both of the new media proved to be less neurotoxic and nephrotoxic. Thus, in equivalent solutions iothalamate salts proved to be less toxic than the diatrizoate salts. The intravenous tolerance of these media was far better than with hypaque M-90. MP 2032 is far too viscous for use as a concentrated medium—

it may find usefulness as a less concentrated contrast agent. MP 1005.2 is sufficiently impressive to warrant trial as an aortographic medium—especially in thoracic aortography.

John H. Foster, M.D.
Department of Surgery
Vanderbilt University
School of Medicine
Nashville, Tennessee 37203

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CLINICAL PROBLEMS AND TOXICITY OF CONTRAST AGENTS*

By WILLIAM H. SHEHADI, M.D.
PORT CHESTER, NEW YORK

THE use of contrast agents in radiography began almost immediately after Röntgen's epoch making discovery.

Success in their use depends on the accessibility of the part to be examined, the properties of the contrast medium employed, the technique of application and the skill and experience of the physician conducting the examination. The gastrointestinal tract is readily accessible to the administration and use of contrast media. The examination of the biliary tract is dependent, in large measure, on the functional activity of the liver. Examination of the urinary tract is dependent on the concentrating capability of the kidneys, while special procedures utilizing complex techniques and accurate timing are needed for the examination of the vascular system, nervous system, and other structures less frequently examined.

The early contrast media were inorganic compounds. Many, including sodium iodide, had a high degree of systemic and/or local toxicity which greatly limited their application and usefulness. The introduction of the two molecular iodine organic compounds heralded a new era; however, a high degree of toxicity and frequent untoward reactions continued to be encountered. The last decade has seen the introduction of three iodinated organic water soluble contrast media (triiodo group). These have been accompanied by appreciable decrease in the incidence of toxicity and side reactions and improvement in radiopacity.

Progress in radiology has, in many areas, centered around the development and use of contrast media. The advances made in urography, angiography and cholegraphy,

in particular, have paralleled those made in contrast media.

Nonetheless, side reactions of varying intensity are still encountered and death following intravascular or oral administration of various contrast agents remains a possibility.

The common denominator to all these contrast agents is iodine. Other factors, however, seem to play a significant role in determining the type and incidence of side reactions, the extent of damage to the body tissues and the organs involved in the transportation and elimination of these contrast agents. Additional significant factors include the structural formula and the size of the molecule, the organ of absorption, transportation or circulation in the body, the dosage and duration of the time applied, the concentration of the contrast material in the blood and the method of elimination.

SPECIAL CONSIDERATION

THE GASTROINTESTINAL TRACT

The contrast media presently in use (Table I) are, for the most part, innocuous. The use of barium sulphate occasionally causes impactions, particularly in the distal colon. Complete obstruction has been observed at times.⁵² These situations may be obviated by discretion in the selection of cases, sequence of examinations and appropriate cleansing of the colon.

The use of water soluble iodinated contrast media (hypaque oral, gastrografin) calls for caution in infants and debilitated elderly patients because hypovolemia may develop due to the osmotic activity of the contrast material in the intestines.^{11, 52-54}

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TABLE I

EVOLUTION OF CONTRAST MEDIA USED IN ROENTGENOGRAPHY OF THE GASTROINTESTINAL TRACT

1896	Lead acetate solution	Becker ³	to visualize stomach	unsuccessful, toxic
1896	Bismuth subnitrate capsules	Cannon ¹⁰	to demonstrate deglutition in the goose	
1897	Bismuth subnitrate paste		in general use	toxic
1904	Barium sulphate	Suggested by Cannon		
1908	Bismuth subcarbonate replaced the nitrate because of the toxicity of the latter			
1910	Barium sulphate	Bachem and Gunther ³	in general use since	nontoxic, colon impaction; obstruction
1956	Water soluble iodinated contrast media (Hypaque oral—Gastrograffin)	Davis <i>et al.</i> ¹¹ and Shehadi ¹²		hypovolemia in infants and debilitated elderly patients

THE BILIARY TRACT

Contrast media for biliary tract examination (Table II) should be rapidly and completely absorbed, selectively excreted by the hepatobiliary system and rapidly and completely eliminated by the intestinal tract.⁵⁵⁻⁵⁷

Disturbances of liver function and/or

extrahepatic biliary obstruction result in delayed, decreased or suppressed hepatobiliary excretion. Thus, the kidneys become the alternate route of elimination. The normal kidney is usually capable of handling this extra burden, if the administered dose is kept at the normal prescribed level.^{47,49}

TABLE II

EVOLUTION OF CONTRAST MEDIA USED IN ROENTGENOGRAPHY OF THE BILIARY TRACT

		Visualization	Excretion
<i>Two Iodinated Compounds</i>			
1924-1925	Tetrabromophenolphthalein	gallbladder	gastrointestinal
	Tetraiodophenolphthalein	gallbladder	gastrointestinal
1940	Priodax	gallbladder	urinary
1944	Monophen	gallbladder	?
<i>Three Iodinated Compounds</i>			
1949	Telepaque	gallbladder and ducts	gastrointestinal (90%)
1952	Teridax	gallbladder and ducts	urinary
1958	Orablex	gallbladder and ducts	urinary
1960	Biloptin	gallbladder and ducts	urinary
	Oragrafin	gallbladder and ducts	urinary
1962	Bilopaque	gallbladder and ducts	gastrointestinal (90%)
<i>Six Iodinated Compounds</i>			
1952-1953	Biligradin forte	gallbladder and ducts	gastrointestinal (90%)
	Cholografin Na, Li, Mg	gallbladder and ducts	gastrointestinal
1956	Duografin-(SH 332)	gallbladder and ducts	gastrointestinal
	Cholografin Mg+Renografin	urinary tract	urinary

It is important, therefore, to consider and evaluate the adequacy of renal function before such contrast media are used. Any contrast medium that is primarily excreted by the kidneys, irrespective of the method of administration, should not be used in the presence of disturbed renal function as there is always the danger of a complete renal shutdown and death.^{7,17,21,51,63}

This has been manifest in the history of the short lived bunamiodyl sodium, which has been reported as the cause of death in several patients, due to suppressed renal function and acute renal insufficiency. Death following the use of other cholecystographic media has also been reported; however, this incidence is negligible.²⁴

Furthermore, the shunting from liver to kidney excretion results in high blood levels of the contrast media. Unduly rapid absorption of the contrast material may also be a contributing factor. Such high blood levels may result in systemic hypotension which may vary from a slight drop in blood pressure to shock. Coronary insufficiency and myocardial infarction have been reported following the administration of iodoalphonic acid and iopanoic acid, associated with vasovagal reflex, bradycardia and hypotension.³⁴

Cholecystographic media given orally may cause nausea, vomiting and diarrhea. A skin rash may occasionally be observed. Mild dysuria is experienced by patients, particularly when the cholecystographic medium used has a preferential renal excretion route. The results of tests for urinary protein may be falsely positive. Hypotension and renal failure are rare, but serious, complications. These are more commonly observed in patients with hepatic or biliary disease and in patients receiving multiple doses or single doses larger than is recommended.

Of the 4 contrasts agents used, orabilex, oragrafin (biloptin), bilopaque and telepaque, the latter still retains the safest record (Table III).

The problems pertaining to intravenous cholegraphy and the administration of cholografin (biligrafin) present a combination of the factors similar to oral cholecystography and the intravascular injection of contrast agents.^{20,58-61}

INTRAVASCULARLY ADMINISTERED CONTRAST AGENTS

For the most part all intravascularly injected contrast agents present the same problems of local and general toxicity, side reactions, complications and tissue damage.

TABLE III
COMPARISON OF ACUTE ORAL LD₅₀ IN MICE

Telepaque	15.800 mg./kg.
Orabilex	2.200 mg./kg.
Oragrafin-Biloptin	
Oragrafin Calcium	2.450 mg./kg.
Oragrafin Sodium	1.700 mg./kg.

INCIDENCE OF DEATH IN MAN				
	No. of Doses Administered	No. of Deaths	Cause of Death	Incidence
Telepaque	22,000,000	7	4—renal damage 1—myocardial infarction 1—liver necrosis 1—deliberate overdose by cancer patient	1/3,000,000
Orabilex	not determined, discontinued in the United States	over 22 cases in 6 years	renal damage	
Oragrafin	621,196	1	anaphylactic shock	1/600,000

TABLE IV
EVOLUTION OF CONTRAST MEDIA USED IN VASCULAR ROENTGENOGRAPHY

1923	Iodized oil injected into the antecubital vein of a living human subject and, under fluoroscopic control, its flow observed into the right heart and then into the pulmonary arteries	Sicard and Forestier ⁶²
1923	Strontium bromide injected into the arteries and veins of the human arm and hand	Berberich and Hirsch
1924	Femoral artery opacified with a 50 per cent solution of sodium iodide, patient under general anesthesia	Brooks ⁸
1927	Cerebral angiography—sodium iodide solution injected into internal carotid artery	Egas-Moniz
The great systemic toxicity and local irritation rendered sodium iodide unusable for safe and satisfactory studies of the vessels		
1929	Translumbar abdominal aortography	dos Santos
1931	Cardiac catheterization with sodium iodide and later with uroselectan	Forssmann ¹⁸
1936	Thorotrast carotid angiography	Lowman
1937	Cardioangiography	Castellanos <i>et al.</i>
1938	Cardioangiography using 70 per cent diodrast	Robb and Steinberg
1941	Aortography following femoral catheterization	Fariñas
1951	Femoral artery catheterization	Pierce
1953	Regional and advanced arterial catheterization technique	Seldinger
1958	Intravenous aortography and arteriography	Evans and Finby

The reported incidence varies in different series (Table IV).^{1, 8, 12, 13, 15, 16, 22, 29, 30, 33, 36, 38, 39, 42, 45, 62}

For the purpose of this study the lymphatic vessels are not included. The intravenous route is used in venography, intravenous arteriography and aortography, and for a study of the urinary and biliary tracts. The intra-arterial route is used for opacification of arterial trunks near the site of injection or their distant branches, performed by direct puncture or selective catheterization.^{18, 19, 35, 50}

THE URINARY TRACT

Intravenously administered contrast medium for the examination of the urinary tract (Table V) should be selectively and rapidly excreted by the kidneys, and sufficiently concentrated by the latter, resulting in adequate opacification of the urinary tract. There is no local tissue damage at the site of injection and pain along the course of the vein hardly ever occurs, but side reactions are observed in approximately 10 per cent of patients examined and the mortality rate is 1/125,000 (Table VI).^{14, 23, 25, 40, 41, 43, 44}

While impairment of renal function may not be a contraindication, all kidney functions may be altered and depressed. In this connection multiple myeloma presents a special problem.^{9, 32, 48}

Several reports have appeared in the literature during the past 10 years of patients with multiple myeloma who died of acute renal failure immediately following or shortly after intravenous urography. In most reported cases, urokon or diodrast was

TABLE V
EVOLUTION OF CONTRAST MEDIA USED IN ROENTGENOGRAPHY OF THE URINARY TRACT

1923	Sodium iodide—excretion urography	Osborne <i>et al.</i> ⁴¹
1929	Uroselectan	Von Lichtenberg and Swick
1930	Abrodil—Skiodan	
1931	Diodrast	
1931	Neolopax	
1933	Hippuran	Swick
1951	Urokon	Wallingford
1954	Hypaque	Hopee and Archer
1956	Renografin	
1963	Conray	

TABLE VI
SIDE REACTIONS AND COMPLICATIONS OF INTRAVASCULAR INJECTION OF CONTRAST MEDIA

Procedure and Type of Examination	Investigators	No. of Cases	Total Side Reactions		Total Deaths		Incidence	
			No.	Per Cent	No.	Per Cent		
Intravascular lumbar aortography translumbar femoral catheter	Mc Afee ³⁸	13,207 12,830 375	98	0.74	37	0.28	1/357	2.8/1,000
Retrograde thoracic aortography	Abrams ¹	1,706	26 severe non-fatal		29	1.7	1/59	17/1,000
Retrograde percutaneous arteriography	Lang ²⁹	11,402	81	0.70	7	0.06	1/1,630	0.6/1,000
angiocardiology	Dotter and Jackson ¹²	6,824			26	0.38	1/262	3.8/1,000
angiocardiology	Finby <i>et al.</i> ¹⁶	4,200			1	0.025	1/4,200	0.25/1,000
cerebral angiography	Lyons ³⁶	2,845	49	1.7	22	0.8		8/1,000
	Lindner <i>et al.</i> ³³	553			6	1.0		10/1,000
	Field <i>et al.</i> ¹⁵	2,000	33 mild 8 severe	1.6 0.4	8	0.4		4/1,000
	Tonniss and Schiefer	12,870	0.24% severe			0.23		2.3/1,000
Intravenous urography	Patterson <i>et al.</i> ⁴²	604	28	4.6	1	0.16		
	Pendergrass <i>et al.</i> ⁴⁴	11,546,000			156		8.6/1,000,000	1/125,000
	Ochsner <i>et al.</i> ⁴⁰	10,000	853	8.53	0			
Intravenous cholangiography	Frommhold and Braband ²⁰				22		3.5/1,000,000	1/300,000
	Shehadi							
	cholografin							
	sodium	500		15.3				
	lithium	50		44.0	0			
	methyglucamine	3,000		7.5				

used, which are good protein binders. Probably poor protein binders, such as hypaque and renografin, may be safer. In this disease there is precipitation of protein within the lumen of the tubules, with accompanying tubular dilatation, gradual mechanical obstruction, glomerular atrophy, and progressive uremia. The kidney may be involved early and renal disease may be a guise under which multiple myeloma may escape detection. In the preparation of the patient for intravenous urography, dehydration due to restriction of fluids and purgation, also abdominal compression which reduces renal blood flow, further aggravate the condition of the kidney. Intravenous urography is, therefore, best avoided in multiple myeloma.

SIDE REACTIONS

Intravascularly administered contrast agents (intravenous—intra-arterial) may

produce adverse reactions of varying intensity and, at times, death (Table VI). The heart, the nervous system and the kidneys are critical areas.

Reactions may be initiated by an inherent histamine liberating capacity of most of the available contrast media. The reactions may be allergic, and include urticaria, angioneurotic edema, laryngeal and/or bronchial spasm or they may be anaphylactoid. Direct toxic effects on the tissues may cause vascular damage with increased capillary permeability and disruption of the blood brain barrier, irritation or damage to nerve structures with convulsions, and transitory or lasting neurologic deficits.

Electrocardiographic changes and disturbances of cardiac rate and rhythm, hypotension, circulatory collapse and shock may occur. Coronary insufficiency and myocardial infarction have been reported. This raises the question of cause and effect.

Kidney damage with proteinuria, elevation of the blood urea nitrogen and/or irreversible renal failure are serious complications. The administration of one or more doses of the contrast medium shortly after the first injection tends to increase the possibility of tissue and organ damage so that the toxicity is related to time, or duration, of application as well as to the quantity of contrast material applied to an organ.

Explanation of these phenomena on the basis of "allergy" and "anaphylactoid" reaction remains, in a large measure, an oversimplification and a mask covering our inadequate and incomplete knowledge, if not ignorance. Thus, the occurrence of untoward reactions remains one of the major factors limiting the use of radiopaque diagnostic agents.

The exact incidence of side reactions is difficult to determine. This is due, in large measure, to the difficulty of evaluating side reactions and to the difference in criteria used by different investigators, making comparisons, at times, impossible. Many side reactions may be minimized by the patient or the observer and the converse is true. A review of the literature and a careful search for unpublished data may yield figures which may be arithmetically more correct than those presently obtained (Table VI). This, however, would not be statistically significant and above all would be of no clinical importance.

In our present state of knowledge, the nature of the toxic action of radiopaque iodinated contrast agents is not understood and the cause of the complex processes manifested in the so-called side reactions remains unknown. The responsible mechanism has not yet been demonstrated. Brilliant animal studies are being done constantly and should be extended even further than heretofore. The results of the LD₅₀ determinations serve as helpful guidelines, but do not give us the answer to the true problem as it applies to the human subject. The results of animal toxicity studies are not necessarily interchangeable with those of the human. There is less variation

in the response of animals of a given species than in the human—where there is likely to be a wide range of variations between individuals, as well as of the same individual at different times. We are, therefore, faced with the necessity of painstaking controlled and extensive human studies, perhaps on a selective basis, before releasing new agents for general use.

Recent studies focus our attention on significant factors which have a direct bearing on the development of side reactions and an index of the toxicity of contrast media.^{4,5,26-28,31,37,46} These include intravascular aggregation of red blood cells, crenation, hemolysis, and protein binding. The latter seems to be related to the structural formula of the contrast medium. This was well demonstrated in urokon, a good protein binder and one of the more toxic of the recent contrast media. The reverse is true in the case of hypaque, a poor protein binder and a contrast medium of very low toxicity. Furthermore, the methylglucamine salts cause fewer and less severe side reactions than do the other salts.

PRELIMINARY OR SENSITIVITY TESTS

The ocular, oral and intradermal tests have been justly discarded as useless. At present, the intravenous sensitivity test is most widely used, though not without its limitations.

Death has occurred in 2 patients following intravenously administered test doses of 1 cc. and 2 cc., respectively. A severe, near fatal, reaction occurred following the intradermal injection of 0.10 cc. as a test dose.^{43,44}

Severe reactions and death have occurred in patients with negative reaction to the preliminary sensitivity test and many with positive reactions to the test did not manifest any untoward reactions when the full dose of the contrast material was administered.

It is impossible to predict beforehand which patient will and which patient will not manifest untoward reactions to the administration of contrast media, although

probably about 10 per cent of all persons to whom contrast media are administered will manifest varying degrees of side reactions. It is believed that patients with a history of allergy, or with a family history of allergy, may be more likely to have adverse reactions. This has not been our experience. Previous injection of contrast material does not sensitize the patient to future doses of the same medium. The patient may develop side reactions of various intensity at one time following the administration of an organic iodine contrast medium, but this may not be the case at another examination. The subject warrants further and more intensive investigation.

PREMEDICATION AND PREVENTION OF UNTOWARD REACTIONS TO CONTRAST MEDIA

The routine premedication with antihistamines (Chlor-Trimeton, Benadryl, etc.) gives a false sense of security and is ineffective in preventing side reactions, as is also premedication with glucocorticoids (Solu-Cortef, Hydrocortone). Recent studies indicate that low molecular weight dextran affords appreciable protection, exerting a stabilizing effect on the red blood cells. Experimental studies indicate that premedication with this substance doubles the LD_{50} and LD_{100} when 90 per cent hypaque is rapidly injected into dogs.⁶

CRITERIA FOR THE IDEAL CONTRAST MEDIUM

The effect of contrast media should be considered in its relation to:

1. The organ or part first involved in the administration or application: (a) site of injection; and (b) site of absorption.
2. The organ or part examined, which is the primary objective of the examination.
3. The organ or channel of elimination. The contrast medium should not produce any systemic reaction nor any untoward effects on the body tissues as it: (a) is introduced into the human body; (b) opac-

ifies the parts to be examined; and (c) is eliminated from the body.

Ideally, though rarely, the organ or part involved in the administration, the organ or part examined, and the organ or part involved in the elimination are the same. This applies to the digestive tract using barium, hypaque or gastrograffin. To a certain extent, these criteria are met in the biliary tract when telepaque and cholografin (bili-grafrin) are used inasmuch as up to 90 per cent of these contrast media are eliminated through the gastrointestinal tract.

Elimination of contrast media through the kidneys often throws an added burden of excretion on a system not involved in the primary objective of the examination and with inherent danger of damaging renal tissues. Therefore, more careful and extensive hepatic and renal function studies should be performed. The liver function tests should include determination of: serum bilirubin (direct and indirect), bromsulphalein retention, alkaline phosphatase, and thymol turbidity. The kidney function tests should include determination of: blood urea nitrogen, creatinine level and creatinine clearance, and routine urinalysis.

On a level of clinical investigation, these tests should be performed on a patient before the administration of the contrast media, at the time of the administration of the contrast media, and shortly thereafter, within 1 to 2 days. Should abnormal findings be detected, these studies should be repeated over a reasonable length of time until they return to normal.

SUMMARY AND RECOMMENDATIONS

Despite the great strides made in the development and evolution of contrast media, the problem of toxicity with resultant untoward side reactions and fatal reactions is still with us. Such untoward side effects seem to be inherent to the organic iodine in the radiopaque contrast media.

As long as such contrast media are used, nontoxicity will probably not be obtained.

Our requirements for improved contrast agents should extend well beyond meeting technical criteria of roentgenographic density and the quality of the shadow as observed on the roentgenograms. It should center on the problems of toxicity with more accurate determination of the processes that take place in the human body between absorption and elimination of the contrast medium, both in the normal and abnormal state.

Accordingly, the following are recommended:

More controlled human studies, with careful evaluation of functional liver and kidney studies, an area hitherto not fully explored.

The continued search for iodine contrast media with a new structural formula which will result in decreasing or eliminating toxicity, or the search for new contrast agents which are not iodine containing, thus eliminating the inherent toxicity that seems to accompany the latter.

Further evaluation of the protective role of low molecular weight dextran or the development of other more protective agents.

The prescribed normal dose, as recommended, should not be exceeded and unnecessary repetition of the dose should be avoided.

An agency be set up on the International level, more appropriately under the direction and guidance of this body, to collect, tabulate and arrange for the recording of the incidence of side reactions and mortality resulting from the use of contrast media and a free exchange of information of valuable data which may or may not necessarily be published.

We should welcome the new, but should accept it with justifiable caution and healthy skepticism. The apparently gratifying initial results of new contrast media may not last long, since usage and time will bring out shortcomings which could not be predicted or anticipated from predetermined studies. This should come neither as a surprise nor disappointment, but should

challenge all our resources for further investigation and research until the ideal has been attained and the safety of our patient completely assured.

Department of Radiology
United Hospital
406 Boston Post Road
Port Chester, New York

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COMPARISON OF SEVERAL METHODS FOR EVALUATING IMAGE QUALITY OF RADIOGRAPHIC SCREEN-FILM SYSTEMS*

By K. ROSSMANN, PH.D.
ROCHESTER, NEW YORK

THE development of a reliable method for assessing the quality of radiographic images formed by screen-film systems is important to the user and to the designer of such systems. A variety of test objects, such as wire mesh and holes, are being employed for subjective evaluations of image quality. However, the validity of extrapolating these evaluations to the usual radiographic image composed of complex aggregates of more or less sharp or diffuse shapes is certainly open to question. The adaptation to radiography of objective methods of image analysis which are well known in photography and optics, such as modulation transfer function analysis, has created new possibilities for the solution of the problem. However, it will be shown by using two selected screen-film systems as examples that quality evaluations by means of modulation transfer analysis, and the visual inspection of wire-mesh and hole radiographs can result in significantly different conclusions.

The appearance of a radiograph results from a complicated interaction of several factors,^{1,2} each of which can be studied separately, but whose relative importance is not known in detail. Experience has shown that the system and image parameters which have an important effect on radiographic image quality are those summarized in Table I. Light diffusion in the screen-film system causes unsharpness which impairs the visibility of fine detail, such as bone trabeculation and small blood vessels filled with contrast medium.

Quantum mottle³ is a fluctuation of

photographic density on the film which is coarse relative to the inherent graininess of the film. It is the photographic image of many randomly located light bursts due to the x-ray quanta absorbed in the screens. Thus, the appearance of quantum mottle is dependent not only on statistical parameters but also on the optical properties of the system as well as on the sensitometric characteristics of the film as indicated by arrows in Table I.

The effects of quantum mottle and light diffusion on the visibility of detail in a radiograph depend on the contrast and configuration of the radiographic images to be detected, as shown in Figure 1. The two screen-film systems with which these test-object radiographs were made had essentially the same sensitometric properties. However, they differed in two important physical aspects: System A, on the left, had better resolution; System B, on the right, absorbed about 2.5 times as many x-ray quanta as the system on the left and imaged the resulting light bursts less sharply. These

TABLE I
FACTORS INFLUENCING RADIOGRAPHIC
IMAGE QUALITY

Light Diffusion	} Radiographic Image Quality
↓	
Quantum Mottle	
↑	
Film Contrast	
↓	
Image Contrast	
Image Configuration	

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From Research Laboratories, Eastman Kodak Company, Rochester, New York.

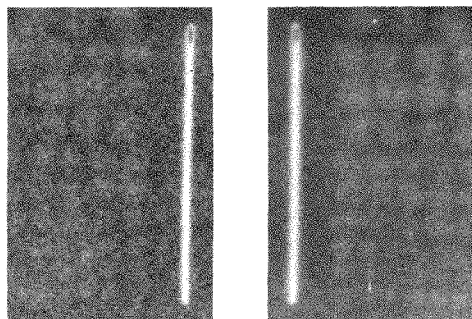


FIG. 1. Radiographs of a test object illustrating dependence of the image quality of screen-film systems on the type of image recorded. Note that the needle image is sharper on the left (System A), whereas the visibility of the beads is better on the right (System B).

differences caused objects which are inherently sharp and of high contrast, such as the needle, to be imaged better by the sharp system on the left. Objects which are inherently of low contrast and unsharp, such as the plastic beads, were imaged better by the less "noisy," unsharp system on the right. This simple example casts grave doubts on the possibility of determining the over-all image quality of screen-film systems by means of a single, uncomplicated measurement. This will be illustrated further by applying modulation transfer analysis, the wire-mesh test, and the hole test to these two systems.

Figure 2 shows the modulation transfer functions (MTF) of the two screen-film systems under discussion. The MTF is essentially a measure of the effect of light diffusion on image quality and is independent of the energy of the exposing x-rays in the usual medical kilovoltage range (50–150 kvp.).^{4,5} The effects of quantum mottle and the sensitometric properties of a film on image quality cannot be determined in this manner. The curves in the figure show that System A is able to resolve higher spatial frequencies than System B. Therefore, System A is the better one, according to the MTF test.

The wire-mesh test was carried out in the usual manner by radiographing patches of mesh of various gauges. Image quality was

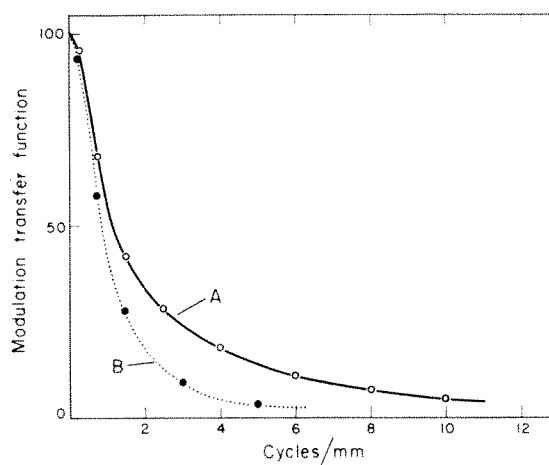


FIG. 2. Modulation transfer function of the screen-film systems used to produce the radiographs in Figure 1.

judged visually from the finest mesh which could just be resolved by the screen-film system. According to the results from this test as summarized in Figure 3, System A is the better one at 70 kvp., and at 120 kvp., in agreement with the MTF. However, the quality of System A at 120 kvp. is lower than its quality at 70 kvp. In fact, System A just resolved the same wire mesh at 120 kvp. as the poorer System B resolved at 70 kvp. This dependence of system quality on kilovoltage is in disagreement with conclusions reached from MTF measurements

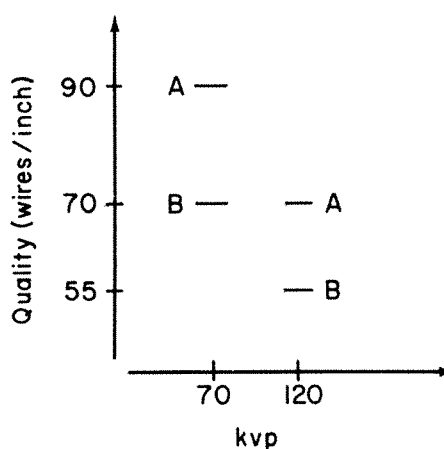


FIG. 3. Image quality of screen-film Systems A and B at 70 and 120 kvp., according to the wire-mesh test.

alone. The reasons for this disagreement can be inferred from Figure 4, which shows on the left a radiograph of wire mesh made with System A at 120 kvp., and on the right the same wire mesh radiographed with System B at 70 kvp. The deterioration of image quality on the two radiographs is due to different physical causes.

The higher kilovoltage and lower light diffusion on the left resulted in reduced radiographic contrast and increased quantum mottle. The greater light diffusion on the right resulted in reduced resolution. The complicated effect of these factors on the resolution of wire-mesh images happened to make the quality of these two systems equal at different kilovoltages—in this case, 70 and 120 kvp. It can hardly be expected that the same result would be obtained with a different image configuration, one not consisting of small, square density patches bounded by lighter lines.

Indeed, this is borne out by the hole test carried out in the usual manner by radiographing holes drilled into a lead plate onto a uniform background exposure. Image quality was judged visually from the smallest hole which could just be detected with certainty at a given subject contrast. Plotting subject contrast against diameter of the smallest visible hole gives the contrast-detail diagrams shown in Figure 5. According to these curves, System B is better than System A at 70 kvp. and 120 kvp. Also, System A at 70 kvp. is nearly equal to System B at 120 kvp. This con-

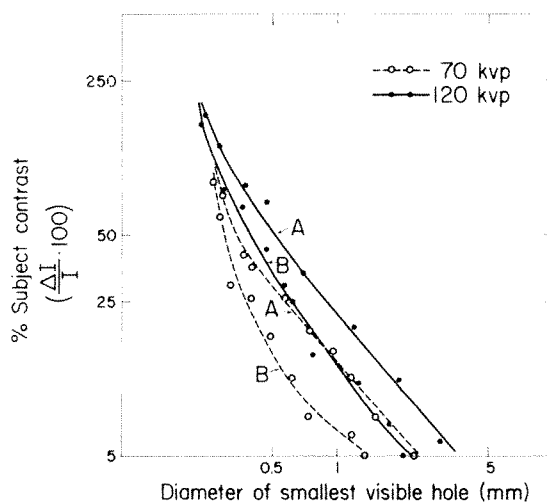


FIG. 5. Image quality of screen-film Systems A and B at 70 and 120 kvp., according to the hole test (contrast-detail diagram).

tradicts the conclusions reached from MTF measurements and wire-mesh tests. Figure 6 shows some typical hole images. Note that the visibility of the holes is determined mainly by their contrast and by quantum mottle. The resolution of the system is not of great importance except as it affects the recording of quantum mottle.

Table II is a summary of the results of the relative quality evaluations of Systems A and B by means of the three test methods. The contradictions evident from the table are not very surprising, considering the specific nature of each test. The MTF is a measure of the effect of light diffusion only; the wire mesh tests the effect of light diffu-

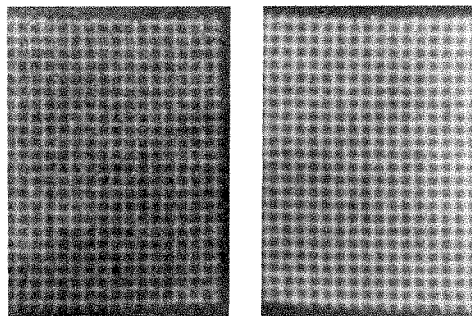


FIG. 4. Radiographs of wire-mesh made with System A (120 kvp.), left, and with System B (70 kvp.), right.

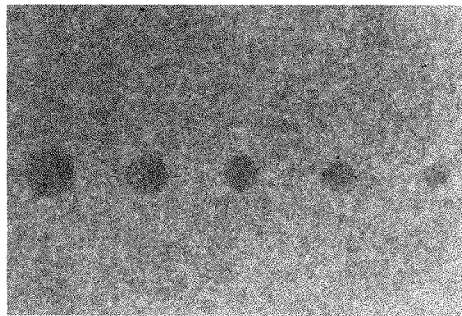


FIG. 6. Typical radiograph of holes in a lead plate used to obtain the contrast-detail diagrams in Figure 5.

TABLE II
RELATIVE IMAGE QUALITY OF SCREEN-FILM SYSTEMS
A AND B ACCORDING TO THREE DIFFERENT
METHODS OF QUALITY EVALUATION

System	MTF ¹ any kvp.	Wire Mesh		Holes	
		70 kvp.	120 kvp.	70 kvp.	120 kvp.
A	X	X	X	O	O
B	O	O	O	X	X

X indicates better system.
= indicates equal quality.
O indicates poorer system.
Note contradictions.

sion (and to some extent, quantum mottle) on the resolution of fine, linear detail of relatively high contrast; the holes test the effect of quantum mottle (and to some extent, light diffusion) on the visibility of low-contrast detail, the detection of which is mainly noise-limited. Since radiographs of the human anatomy usually contain a mixture of image types, ranging from those that are noise-limited in visibility to those that are resolution-limited, it can hardly be expected that any one simple test using a single image type will suffice to measure the over-all quality of screen-film systems.

Of course, the particular screen-film systems discussed here were chosen especially to emphasize the problems arising in the measurement of radiographic image quality. However, basic physical and psychophysical phenomena were involved, so that it is valid to draw the general conclusion that radiographic image quality depends not only on parameters of the imaging system, but also on the type of image being recorded. Hence, it is not possible, in general, to express the over-all quality of screen-film systems by a single number. In fact, "over-all quality" has no meaning, as was illustrated in Figure 1. Much work will have to be done to enable us to understand the recording of "typical" radiographic images, before a general, objective or sub-

jective method of quality evaluation of screen-film systems or, for that matter, of any radiological imaging device can be recommended.

SUMMARY

The appearance of a radiograph results from a complicated interaction of several factors, each of which can be studied separately, but whose relative importance is not known in detail. It is difficult, therefore, to develop a general technique for measuring radiographic image quality which holds for all types of images under any imaging condition.

To illustrate this point, results obtained from several often-used methods of quality evaluation are compared: Contrast-detail diagram, modulation transfer function, and wire-mesh test.

It is concluded that image-quality evaluations by means of modulation transfer analysis and the visual inspection of wire-mesh and hole radiographs can result in significantly different results.

Research Laboratories
Eastman Kodak Company
Rochester, New York 14650

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ASSESSMENT OF RADIOLOGIC IMAGING*

By EARLE C. GREGG, PH.D.
CLEVELAND, OHIO

THE present day trend of using very small exposures in diagnostic radiology has served to emphasize a problem basic to many fields of endeavor: namely, the extraction of information from a statistically varying signal in the presence of noise. For many years such a problem has been of great concern in communication engineering and the enormous advances in that field have been due in no small part to an extensive theoretic development of the information content in various signals and its loss by transmission through subsequent complex systems. The use of electronic image amplifiers, television techniques and computers in radiology—all of which involve converting a two dimensional image into a one dimensional time varying electrical signal and its subsequent reconversion to meaningful data—illustrates the fact that all these systems are equivalent and that the techniques and theories of communication engineering are directly applicable to this problem.

That the image formed in radiography and its subsequent interpretation by the eye are limited by statistics has been noted by many.^{4, 8, 11, 20, 23, 24} These limitations have generally been applied to the concept of contrast C or its reciprocal, contrast sensitivity, c . On the other hand, the term "resolution" r has been recognized to be unsatisfactory since it is subject to many interpretations and types of measurements—the most common being the reciprocal of the minimum detectable distance between two lines under conditions of maximum contrast. For many reasons, the concept of "modulation transfer function" has been borrowed from the field of optics¹³ and communication engineering^{9, 15} and has been suggested as a better criterion of perfor-

mance of radiologic systems than resolution.^{2, 16}

Under any circumstance, the radiologist has been faced with two separate and apparently distinct criteria of his pictures: namely, contrast range and resolution (or transfer function)—each varying in a different manner amongst various systems.

The first attempt to provide one number as a performance criterion was by Hay¹¹ who proposed the product (σ) of the resolution and the contrast sensitivity which he termed the information index. A second proposal was made by Friedell and Gregg⁸ through a comparison with information theory that provided a number called the information capacity that was of the form $r^2 \log(1+c)$ where c was evaluated for the resolvable area determined by r . This formulation has the advantage of bearing a direct relation to the concepts so important in communication engineering and has also proved of value in optimizing the performance of special systems.¹⁰ This has not been possible with the information index.

It is apparent that the formulation for information capacity weights the influence of the resolution relative to the contrast much more than the formulation for the index. Although it was proposed on different grounds, this is in apparent agreement with the subjective feeling that, for the mere conveyance of information, contrast is relatively unimportant. Regardless, neither of the above criteria emphasized the fact that the terms "resolution" and "contrast" are intimately related in statistically limited processes and that it is possible to devise a single criterion without reference to any such rather arbitrary terms. That the two are related is apparent from the fact that the ability to "resolve" depends upon

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From the Department of Radiology, Western Reserve University, Cleveland, Ohio.
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the statistical fluctuations in the "resolvable" area.

It is the purpose of this paper to develop a formulation based on the tenets of information theory that directly relates both the physical and statistical parameters of a given system. This, in turn, leads to a single criterion of system performance, a possible estimate of the size and complexity of associated systems, and, finally, an insight of possible system improvement.

SIGNAL TO NOISE RATIO

It is obvious that, at the plane of any detecting device used in diagnostic radiology, one is confronted with a two dimensional distribution of x-ray photons that bears some relation to the information of medical interest. Since the stream of photons is varying randomly in both space and time, the only available measure of such a two dimensional distribution is the average number per unit area detected (or absorbed) during the time of measurement. It is fairly obvious that if we divide the detecting plane into a number of small areas, each with area A , then the number detected in each area will be different simply because of the randomness of the original photon beam.

This variation in the average number detected per unit area may then be considered to be the "noise" inherent in the measurement and the average number to be the "signal."

Putting aside for the moment the question of the detecting process, we see that if the original photon beam has an average of S_0 photons per unit area, then the *rms* variation in each area A is $\sqrt{S_0 A}$. Thus, the original signal to noise power ratio R_A becomes $(S_0 A)^2 / S_0 A = S_0 A$. Another way of looking at this is to say that in each measured area A , we calculate an S_0 with an *rms* variation of $\sqrt{S_0 A}$ in our calculation. Thus, $R_A = S_0^2 / S_0 A = S_0 A$ as before. In any case the signal to noise power ratio diminishes as the test area decreases. Interestingly, this has been noted when scanning uniformly exposed photographic films

with apertures of various sizes and the ratio $S = R_A^{1/2} / A^{1/2}$ has been termed the "Selwyn Coefficient" and used as a measure of the granularity of films.¹⁴

Similarly, if N_0 photons per unit area that do not arise from the pattern of interest are scattered into the detector area during the same length of time, we have for the true signal to noise power ratio $R_A = S_0^2 A / (S_0 + N_0)$.

SIGNAL TO NOISE RATIO WITH AMPLIFICATION

Consider now the first portion of Figure 1 where a signal of $(S_0 + N_0)A$ (particles) is incident on a device of particle gain G_1 . If this stage of gain is both noiseless ($N_1 = 0$) and not in itself a statistically varying quantity, we would observe at the output a signal of $G_1 A (S_0 + N_0)$ with a noise amplitude of $G_1 (S_0 A + N_0 A)^{1/2}$ which would produce the same signal to noise ratio as the input signal. This results, since we may consider the output to occur in coherent "clumps," with the frequency of the clumps being the same as the rate of arrival of the incoming particles.

However, in the process of conversion gain considered here, G_1 is really a statistically varying quantity in itself since there is only a chance that our incoming particle will be absorbed to produce a subsequent photon or electron. Thus, we observe at the output a variation $G_1 (S_0 A + N_0 A)^{1/2}$ due to the source itself reflected through a constant G_1 and $[G_1 A (S_0 + N_0)]^{1/2}$ due to the am-

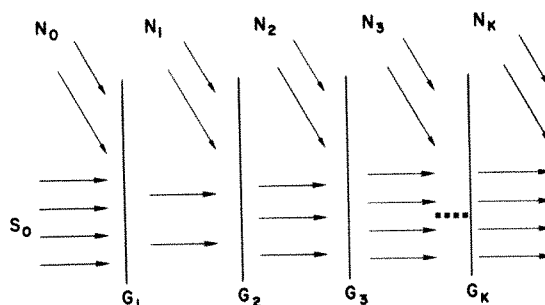


FIG. 1. Idealization of K devices in series each with particle gain G_n and introducing extraneous noise N_n per unit area.

plified signal if the source itself were constant. Since the noise powers add, we have for the output noise power,

$$N^2 = G_1^2(S_0A + N_0A) + G_1(S_0A + N_0A)$$

and, for the signal to noise power ratio,

$$R_A = \frac{S_0^2A}{S_0 + N_0} \frac{G_1}{1 + G_1}.$$

This will produce the same R_A for $G_1 \gg 1$ but a materially different ratio for $G_1 \ll 1$, illustrating the fact that below a certain number of photons per clump, the variation in the total number of photons determines the noise and not the frequency of the clumps. Generalizing for n stages of gain each introducing N_n additional noise particles per unit area, we ultimately find

Regarding the time of observation, it is obvious that if T_s is the shortest time of observation and if the photons are arriving at the rate R_0 per unit area, then $S_0 = \int_0^{T_s} R_0 dt = \text{total exposure}$. Since this exposure may occur in bursts due to half-wave pulsed sources, it is important to remember that the noise in subsequent devices may be generated continuously. If these devices are on for $T_s^1 (> T_s)$, then the noise to signal power ratio ($1/R_A$) terms involving N_n increase as T_s^1/T_s . For pulsed radiation of length T_0 , we see $T_s = pT_0$ where T_s is not the total "on-time" of the radiation and the total number of pulses. For visual observations, T_s^1 is the storage time of the eye (0.2 sec.) which will be discussed later. Thus, unless the electronic devices are "gated on" only during the radiation

$$\begin{aligned} \frac{1}{R_A} = \frac{1}{A} & \left\{ \frac{S_0 + N_0}{S_0^2} \left[1 + \frac{1}{G_1} + \frac{1}{G_1 G_2} + \cdots + \frac{1}{\prod_{k=1}^n G_k} \right] \right. \\ & + \frac{N_1}{S_0^2 G_1^2} \left[1 + \frac{1}{G_2} + \frac{1}{G_2 G_3} + \cdots + \frac{1}{\prod_{k=2}^n G_k} \right] \\ & + \frac{N_2}{S_0^2 G_1^2 G_2^2} \left[1 + \frac{1}{G_3} + \frac{1}{G_3 G_4} + \cdots + \frac{1}{\prod_{k=3}^n G_k} \right] + \cdots \\ & \left. + \frac{N_n}{S_0^2 \prod_{k=1}^n G_k^2} \right\}. \end{aligned} \quad (1)$$

It is obvious that the detected true signal to noise power ratio varies as A , which is as expected. Assumptions tacit to the above derivation are that all noise sources are in-

bursts, continuous radiation will produce the lowest noise to signal ratio.

Returning to Equation 1, we see for noiseless gains

$$\frac{1}{R_A} = \frac{1}{A} \left[\frac{S_0 + N_0}{S_0^2} \right] \left[1 + \frac{1}{G_1} + \frac{1}{G_1 G_2} + \cdots + \frac{1}{\prod_{k=1}^n G_k} \right]. \quad (2)$$

dependent of the signal of interest and that all devices are on the same length of time.

We shall define the over-all gain of system G to be

$$\frac{1}{G} = 1 + \frac{1}{G_1} + \frac{1}{G_1 G_2} + \dots + \frac{1}{\prod_{k=1}^n G_k} \quad (3)$$

For $G_1, G_2 \dots G_n \gg 1$, Equation 2 reduces to $R_A = A S_0^2 / (S_0 + N_0)$, which is the same as that of the source itself at the detector plane. However, if $G_1 \ll 1$, this alone controls the ratio while if only $G_k < 1$, this may not, depending on the magnitude of the prior gains. Unfortunately, in most radiologic devices, G_1 is the initial absorption of the x-rays which is much less than 1 and, hence, probably controlling. The same considerations hold for the noise sources N_n , except that these are generally introduced later in the system (*i.e.*, $N_1 = N_2 = 0$ for image amplifiers and fluorescent screen-image orthicon systems).

It is most important to note that optical magnification is not a photon gain but that optical aperture (solid angle of acceptance) is. Optical aperture may be treated as a statistically varying gain since we are dealing with a two dimensional randomness and there is only a chance that a given photon will enter an aperture. On the other hand, both optical and electron optical magnification can change the defined signal to noise ratio through the scale factor by which A is measured relative to S . If the measurement of A is always referred back to the object at which point S_0 is also specified, then the signal to noise ratio will be constant and independent of the magnification. Thus, when an image amplifier tube which reduces the image on its output screen is imaged on a film through lenses, the over-all signal to noise ratio per unit object area will be independent of the fact that a chain of reduction and magnification was used except, of course, for the apertures involved.

It is to be noticed that the eye may also be treated as a device with gain and that the very low value is due to the small aperture

and low quantum efficiency.^{18,19} However, the gain changes with illumination level due to the change in pupillary diameter, but this is a very slow process compared with the changes one encounters when scanning an image. Thus, in all cases the aperture resulting from a given average illumination will be used.

It is to be emphasized that only aperture effects and efficiencies will be treated here since the purpose of this presentation is to calculate the information capacity up to the final optical image on the retina and not that of the eye-brain system. Now, when an ideal (lossless) lens is used in conjunction with the eye under the circumstances that the exit pupil of the lens is larger than the pupil of the eye, it can be shown that the effective aperture of the eye at normal viewing distance is increased by the area magnification of the object so that the apparent brightness is unchanged (Abbe's Law). Thus, if an image amplifier reduces the image area by a factor of 100, the effective aperture of the eye is increased by a factor of 100 when used in conjunction with a lens that restores the image to its original size. This means that under these circumstances G_k for the eye must be increased by the ratio of the reduction in object area. This effect has been termed "brightness gain" when discussing image amplifiers, but it is to be noted that it holds only for viewing by the eye and not for real imaging on film. The same effect could occur optically if the reduced image were first projected on a perfectly diffusing screen and this new image viewed by the lens-eye system.

In Table 1, the values for x-ray emulsions and fluorescent screens were determined experimentally by measuring the absorption of the radiation from Tm^{170} while those of the electronic processes are "best guesses" from the literature.

When one calculates the gain of the over-all systems under consideration by inserting the appropriate gain values in Equation 3, it becomes apparent that the intermediate gains need not be known too accurately.

TABLE I

Absorption of X-ray Photons	Gain
X-ray Emulsion	0.04
Fluorescent Screen (film) Intensifier	0.40
Fluorescent Screen (visual)	0.80
Fluorescent Screen (image amplifier)	0.05
Conversion	
Absorbed X-ray Photons to Effective Grains	
Very low and very high energies	1
Medium (diagnostic) energies	≈ 3
Absorbed X-ray Photons to Forward Scattered Light (screens)	2,500
Light Photons to Grains in Emulsions	0.25
Light Photons to Electrons (image amplifiers)	0.1
60 kv. Electrons to Forward Scattered Light	700
Eye (plane surface at 25 cm.)	
300 ft.—lamberts	6.25×10^{-7}
20 ft.—lamberts	2.9×10^{-6}
1 ft.—lamberts	1.6×10^{-6}
10^{-2} ft.—lamberts	3.3×10^{-6}
10^{-4} ft.—lamberts	4.5×10^{-6}

MODULATION TRANSFER FUNCTION AND STATISTICS

The modulation transfer function (also known as aperture response, frequency response, Fourier spectrum, contrast transfer function, power transfer function, etc., all of which may have the terms sinusoidal or sine wave prefixed) is merely a mathematical device that allows the calculation of the radiation intensity distribution at the detector in a known system from a given distribution of incident radiation. Similar devices are the point spread function and the line spread function. Knowledge of any one of these three functions will allow the calculation of the other two.¹³ For reasons of mathematical convenience and manipulation, the use of the modulation transfer function in terms of the spatial wave number K has been preferred. It is, however, much more difficult to measure directly.

For convenience in derivation, we shall consider the one-dimensional case shown in Figure 2 where we have a source of radia-

tion that produces an intensity of S_y^1 photons per centimeter at an absorber so shaped that it produces sinusoidally varying signal E of amplitude a at its output. Since we wish to avoid the concept of negative signals, we shall assume the absorber to be infinitely thin at its minimum, leading to the expression

$$E = \frac{S_y^1}{1+a} (1 + a \cos 2\pi K^1 X),$$

where $K^1 = 1/\lambda^1 =$ number of absorbing lines per unit length and $0 < a < 1$. In television it is common to speak of line number which is the number of half-cycles in a unit length. Thus $N' = 2K'$. If now a detector is placed at the exit side of the absorber, it will also produce a sinusoidal response but not necessarily of the same amplitude nor of the same wavelength. The detector response may be stated as

$$D = D_0[1 + b(K) \cos 2\pi KX],$$

where again $0 < b(K) < 1$.

It is important to note that the observed wavelength may be different only because of geometric magnification, while the observed amplitude can depend on both the geometry and the radiation scattering and detecting processes in the system. In radiologic systems, one is confronted with distortions in the detector (*i.e.*, film or fluorescent screen) which change the amplitude response and with distortions in the initial radiation geometry (*i.e.*, a finite focal spot)

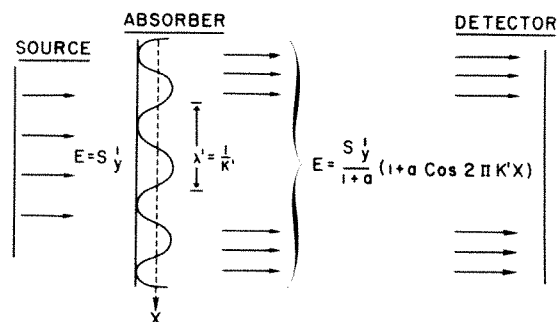


FIG. 2. Schematic drawing for definition and determination of modulation transfer function.

which affect both the amplitude and wavelength, depending on the position of the absorber, source and detector. For purposes of convenience, we shall refer all measurements of wavelength to the plane of the detector, recognizing that such is related to measurements at the plane of the absorber through the geometric magnification.

If, now, in the above example we change the wavelength λ^1 of the absorber but keep the amplitude a constant, we should observe a $b(K)$ that changes with K . The modulation transfer function $\tau(K)$ is simply the function $b(K)/a$ so normalized that $b(0) = a$. Thus, we may rewrite the above as

$$D = \frac{S_y}{1+a} [1 + a\tau(K) \cos 2\pi KX],$$

where S_y is now the number of absorbed or detected photons per unit length (product of incident photons per unit length and the photon gain of the detector) and a is simply a constant representing the amplitude and subject to the restriction $0 < a < 1$. The observed amplitude response is plotted in Figure 3.

Now, the total number of initially transmitted photons making up one image of this repeating pattern is

$$\frac{S_y \lambda}{1+a} = S_y / K(1+a),$$

while the number of photons in the first half of the image is

$$S_1 = \frac{S_y}{2(1+a)K} \left(1 + \frac{2a\tau(K)}{\pi} \right)$$

and the second half

$$S_2 = \frac{S_y}{2(1+a)K} \left(1 - \frac{2a\tau(K)}{\pi} \right).$$

In order to assess a , the parameter of interest, we would for a given K and $\tau(K)$ take the difference

$$S_1 - S_2 = \frac{2S_y a \tau(K)}{\pi(1+a)K}.$$

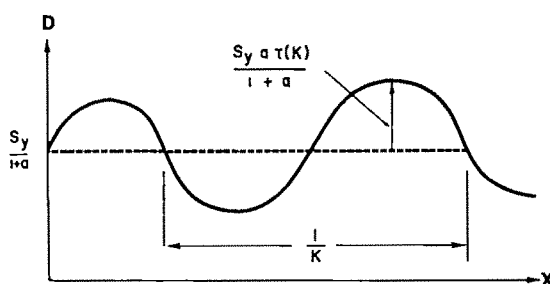


FIG. 3. Particle density amplitude at detector in Figure 2.

For truly random events, the *rms* uncertainty (noise amplitude) in $S_1 - S_2$ is

$$\sqrt{S_1 + S_2} \quad \text{or} \quad \sqrt{\frac{S_y}{(1+a)K}},$$

which is also the *rms* deviation in the total (average) number of photons in each K interval. Thus, the signal power $(S_1 - S_2)^2$ to noise power ratio in each K interval would be

$$\left(\frac{S}{N} \right)_K = \frac{4S_y a^2 |\tau(K)|^2}{\pi^2(1+a)K}.$$

The over-all average density of the detected beam is $S_d = S_y / (1+a)$ which produces

$$\left(\frac{S}{N} \right)_K = \frac{4S_d a^2 |\tau(K)|^2}{\pi^2 K}.$$

If we should now add a second set of random events, N_y photons per unit length that are not modified by $\tau(K)$ (i.e., scatter into an ideal detector), it is simple to show that

$$\left(\frac{S}{N} \right)_K = \frac{4S_y^2 a^2 |\tau(K)|^2}{\left(\frac{S_y}{1+a} + N_y \right) (1+a)^2 \pi^2 K}.$$

If we assume that $N_y = \sigma S_y / (1+a)$, we then find

$$\left(\frac{S}{N} \right)_K = \frac{4S_d a^2 |\tau(K)|^2}{(1+\sigma) \pi^2 K},$$

where σ is the scatter coefficient.

Now let a second transfer $\tau'(K)$ take place. It is obvious that every grating

space K produces an effect $\tau(K)\tau'(K)$ on the K' th amplitude. Thus, the total signal to noise power ratio becomes

$$\left(\frac{S}{N}\right)_K = \frac{4S_dGa^2}{(1+\sigma)} \frac{|\tau^*(K)|^2}{\pi^2 K}, \quad (4)$$

where

$$\tau^*(K) = \prod_{m=1}^n \tau_m(K)$$

and G is the reduction in signal to noise power ratio (gain) for the successive processes.

Without attempting to construct a visual picture of a two dimensional grating of amplitude a , it is possible to mathematically hypothesize a grating that sinusoidally varies with linearly increasing area just like the one dimensional grating varied with distance. The two dimensional modulation transfer function, $\tau(K_x, K_y)$ or $\tau(K_r, K_\theta)$, would then be the ratio of the observed amplitude of detected signal to incident signal for a given spatial frequency variation of area so normalized that $\tau(0,0)=1$. Likewise, the basic "bins" over which we would integrate our detected counts would be $1/K_x K_y$. Figure 3 still would apply but with the x axis replaced by area A . Now, Mertz and Gray¹⁵ have shown that $\tau(K_x, K_y) = \tau(K_x) \tau(K_y)$ and/or $\tau(K_r, K_\theta) = \tau(K_r) \tau(K_\theta)$ so that, proceeding as before, we find

$$\left(\frac{S}{N}\right)_{K_x, K_y} = \frac{4S_0^1Ga^2}{(1+\sigma)(1+a)} \frac{|\tau(K_x)\tau(K_y)|^2}{\pi^2 K_x K_y},$$

where S_0^1 is the incident photon flux density while the average detected flux density $S_0 = S_0^1/1+a$.

For the isotropic case when $\tau(K) = \tau(K_x) = \tau(K_y)$

$$\begin{aligned} \left(\frac{S}{N}\right)_K &= \frac{4S_0Ga^2}{\pi^2(1+\sigma)} \frac{|\tau(K)|^4}{K^2} \\ &= Ha^2 \frac{|\tau(K)|^4}{K^2}, \end{aligned} \quad (5)$$

where

$$H = \frac{4S_0G}{\pi^2(1+\sigma)}$$

or, more generally,

$$H = \frac{4}{\pi^2} R_0,$$

where R_0 is the signal to noise power ratio per unit area. For $a=1$, this ratio (Equation 5) is the maximum number of *rms* noise power steps possible at any given K for a signal that sinusoidally ranges from no absorption to complete absorption.

INFORMATION CAPACITY

Extensive theoretical work in the field of communication engineering^{1,9,22} has led to the following formula for the information capacity of an electrical channel:

$$I = 2WT \log_2 N \left(1 + \frac{P_s}{P_n}\right)^{1/2} \text{ bits/unit time, } (6)$$

where P_s is the mean square signal amplitude (signal power), P_n the mean square noise amplitude (noise power), $2WT$ the number of independent samples (W bandwidth, T time) and N is some constant depending upon the risk of error which can be tolerated. It is important to note that the above formulation requires: (1) that the noise is gaussian, stationary and ergodic; (2) that the signal and noise powers are additive and statistically independent; and (3) for $N=1$, that the signals are optimally coded (presumably gaussian). There has been some argument that film and screen granularity may not be gaussian; however, measurements¹⁴ have established such film and screen noise to be close to gaussian as long as the scanning aperture is reasonably large compared to the grain size. As we shall see, this will be the case here since the resolution is usually limited by the x-ray focal spot much before grain size becomes important. Regarding (3), it is apparent that at this time we are not interested in methods of "coding" information but rather in the capacity of a system that records and "decodes" a given image for which the coding has already been established. A rather naive approach is to imagine the image to be divided into an

array of the smallest resolvable areas A , each of which can contain a signal of maximum power P_s and noise of power P_n . Then, rewriting the above, we would have

$$I = \frac{1}{A} \log_2 N \left(1 + \frac{P_s}{P_n} \right)^{1/2} \text{ bits/unit area, (7)}$$

which would then be a measure of all the combinations of possible amplitudes per unit area in such an array ($1/A$ is the number of such areas per unit area). Now, the ability to measure and specify P_s in the presence of P_n must be taken into account. Since the signal in our case really consists of a group of random events, we only have a certain probability that a given observed change is real and not accidental. If the change is only one standard deviation, then the chance that this is real is only about 60 per cent; for two standard deviations, about 95 per cent; and 3 standard deviations, about 99.7 per cent. For convenience, we shall assume $N^2 = 1/10$ which results in amplitude steps of about 3 standard deviations. Examination of Equation 7 shows, however, that this formulation has the difficulty that the factor A^{-1} controls the expression much more strongly than the log term and, as we decrease A , I increases very rapidly. We ultimately reach a situation where the exposure of one region influences the signal in another region and we are confronted with what is termed "inter-symbol" interference. This difficulty, however, may be overcome by performing the calculation in Fourier transform space where all the messages are orthogonal to each other and, hence, cannot interfere. From the derivation in the previous section, we then see that the term

$$\log_2 N \left(1 + H \frac{|\tau(K)|^4}{K^2} \right)^{1/2}$$

represents the information in an area $(dK)^2$ and, since information from different areas is additive, we may state that

where the integration is only over the first quadrant since negative values of K are not allowed in this formulation. It is to be noted that the term $|\tau(K_x)\tau(K_y)|^2$ allows the use of negative values of τ . Such negative values merely represent a phase shift in the image and do not reduce the information capacity.

Usually, in optics and communication engineering, the upper limit is infinity. In this case, however, we are concerned with statistical fluctuations and we note that for an error of less than 1 per cent (3 standard deviations) we must confine our measurements to the range, where

$$H \frac{|\tau(K_x)\tau(K_y)|^2}{K_x K_y} > 10.$$

It is obvious that since H is really determined by the initial photon flux density, for a given $\tau(K)$ the upper limit becomes smaller the smaller H . It must be remembered that $\tau(K)$ is (and should be) determined experimentally under the conditions of infinite flux but that the above limit on maximum observable resolution of area is determined by the statistical conditions under which the system is finally being used. With the exception of the limits and the use of N , the above expression is almost identical to that derived by Fellgett and Linfoot⁷ when considering optical images. According to Jones¹⁴ and Fellgett and Linfoot,⁷ if, in optical imaging, the noise and signal are not strictly gaussian, the ratio of the power or Wiener Spectra may be substituted for H . While such considerations could be included here, this complication did not seem necessary for the systems under consideration.

Recognizing the fact that the modulation transfer function for finite x-ray spots is not isotropic [*i.e.*, $\tau(K_x) \neq \tau(K_y)$],⁸ we shall proceed to ignore this fact as not too important at this time and derive an expression

$$I = \frac{1}{2} \int_0^{K_m} \int_0^{K_m} \log_2 N \left(1 + H \frac{|\tau(K_x)\tau(K_y)|^2}{K_x K_y} \right) dK_x dK_y \text{ bits per unit area, (8)}$$

for the isotropic case. Letting $\tau(K_x) = \tau(K_y) = \tau(K)$ and $K_x^m = K_y^m = Km$, we have, after integrating the above expression and neglecting the digit 1 in the log term because of the limitation on the term involving H ,

$$I = \frac{K_x^m K_y^m}{2} \log_2 \frac{H}{10} + \frac{K_y^m}{2} \int_0^{K_x^m} \log \frac{\tau(K_x)^2}{K_x} dK_x + \frac{K_x^m}{2} \int_0^{K_y^m} \log \frac{\tau(K_y)^2}{K_y} dK_y \quad (9)$$

$$= \frac{Km^2}{2} \log_2 \frac{H}{10} + Km \int_0^{Km} \log_2 \frac{\tau(K)^2}{K} dK,$$

where Km is determined by the condition

$$H \frac{|\tau(Km)|^4}{Km^2} = 10.$$

This limiting condition really determines the minimum resolvable area whose reciprocal is Km^2 and this value of Km will be called the "apparent" resolution. For a system with $\tau(K) = 1$ for all K , it follows that Km varies as $\sqrt{H}$ or the signal to noise amplitude ratio. Using the eye as a spatially integrating detector and repeating bar patterns with a large bandpass system, Coltman and Anderson⁸ found the above dependence of resolving power on signal to noise amplitude ratio to hold over a fairly large range. It is obvious that Equation 9 may also be applied to scintiscanning and other such systems with statistical limitations.

Again, if we have a system in which $\tau(K) = 1$ for all K , Equation 9 reduces to $I = 1.43 H/10$ which states that the information capacity increases linearly with photon density as might be expected. However, as will be demonstrated later, the influence of any practical $\tau(K)$ becomes so severe that, at higher values of H , the capacity varies as $\log H$. For the subsequent calculations and data, it was found for all experimentally determined transfer functions that $\tau(K) = 1$ for $0 < K < 0.1$ lines per mm. Using this in the above expression and changing to the base 10, we find

where now the integration may be performed numerically and Km in lines per mm. determined graphically for given incident photon densities (per sq. mm.) and assumed values of G .

One last point is that when various conversion devices are involved that are non-linear in nature (*i.e.*, film), the above expressions must be modified to completely account for such effects. While many nonlinearities can be minimized by methods suggested by Jones¹⁴ for recording on film, it is felt that these effects are neither too severe in the systems under consideration in this paper nor too important since they would only modify the expression inside the log term and hence have a very reduced effect. Under any circumstances, complete linearity has been assumed for the subsequent calculations.

DATA AND CALCULATIONS

Figure 4 is a graph of some typical experimentally determined modulation transfer functions^{2,5,16,17} where it is to be noted that only the function for the finite x-ray spot has repeating zeros along the K axis. This function is really negative between the first two zeros but has been folded upwards. Also, this particular function was obtained for a 2 mm. focal spot and originally plotted for the case where the object was half-way between the source and detector. In Figure 4 the scale was changed to the more realistic case of 100 cm. source-object distance and 10 cm. object-detector distance. No object motion has been included which, of course, would make the function much worse.¹⁶ The scales have not

$$I = 1.66 Km^2 [\log_{10} H - 1] + 0.47 Km + 3.32 Km \int_{0.1}^{Km} \log_{10} \frac{\tau(K)^2}{K} dK \text{ bits per sq. mm.}, \quad (10)$$

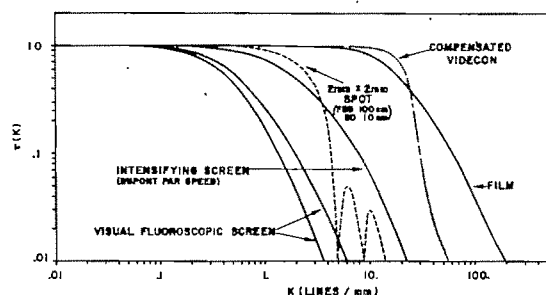


FIG. 4. Some experimentally determined modulation transfer functions.

been changed for the functions describing the fluorescent screens and film.

Also shown is the transfer function for a compensated videcon tube (4.5 mc. bandwidth). By compensated is meant an electrical network that corrects for the high frequency fall-off which in turn is reflected in the transfer function. We shall assume the same function for an image orthicon as well since the compensation may be designed to produce the same frequency response.

While it is not pertinent to these calculations, Figure 5 shows a replot of all the data except the videcon to a θ scale so normalized that $\theta = \pi$ at the first zero for all the functions. It is most interesting and perhaps significant that all detectors including film fall on the same curve, which is much different from that for the x-ray spot alone which fits a $\sin \theta / \theta$ distribution quite well.

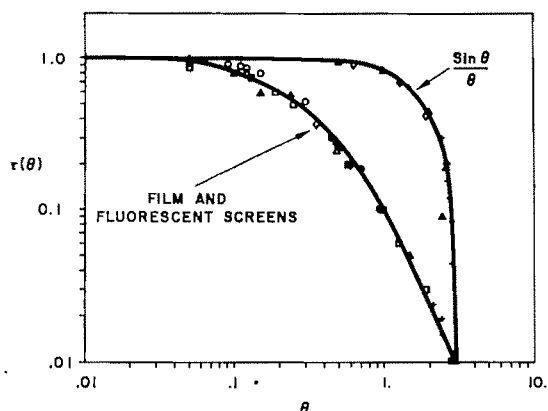


FIG. 5. Data of Figure 4 replotted on a normalized θ axis.

No reasonable analytic function could be found for the screen and film detectors.

In examining systems, we, of course, are interested in the product of all the modulation transfer functions involved and Figure 6 shows the function $\tau(K)$ for the x-ray focal spot combined with film alone, film plus intensifying screen and, finally, with a direct view fluorescent screen. It is to be understood that the product of the transfer functions should be used only when the separate operations can be directly superposed. In some cases where they are separated and scatter can occur (*i.e.*, between intensifying screens and emulsions), it is better to use one function determined for the complete system. The difference, however, should be small in these practical cases and we shall ignore them for lack of better data.

Since there was no modulation transfer function available for an image amplifier tube, one was manufactured by assuming that being thinner, the output phosphor is of slightly better quality than that of film intensifying screens. However, since the

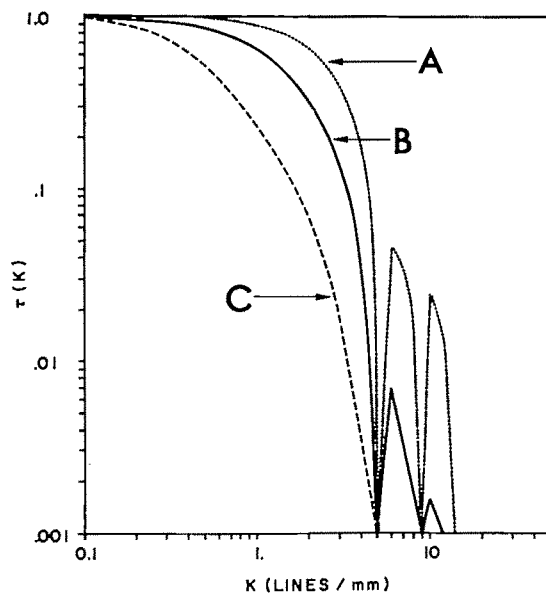


FIG. 6. System modulation transfer functions compounded of 2 mm. x-ray focal spot plus (A) film, (B) film and intensifying screen and, (C) visual fluoroscopic screen.

electron image is reduced in size, the scale of the K axis should be changed by the same ratio as the linear dimensions. Thus, for a typical image amplifier, we arrive at a transfer function about the same as that for visual fluoroscopic screens. This, of course, neglects any effect of the electron-optics which would make it worse. Estimates of line resolution of typical image amplifiers under high flux conditions agree reasonably well with the above assumptions. Unfortunately, most measurements reported to date do not list all the conditions of the test so that an accurate comparison could not be made.

Regarding the use of film recording with image amplifier tubes, we note that since the film and optical system have their own transfer functions and effective apertures, the additional operation can only degrade the over-all capacity. For the storage of a 220 mm. object on 8 mm. film, this is a linear scale reduction of almost 35 which changes the transfer function of film to nearly that of a visual fluoroscopic screen. The product of all the functions then produces a total transfer function with a 0.01 cut-off intercept of about 2 lines/mm. which obviously lowers the capacity. This effect becomes less as the film size increases. Similar considerations apply to videcon and orthicon conversion systems where the videcon has an 11 mm. input screen while that of the orthicon is 36 mm. For average quality optical lenses, the effect of the transfer function may be ignored.

Regarding the aperture effect of the imaging optics, we note that for the chain of amplifications involved and for less than a 10 per cent effect in the signal to noise ratio, the optical aperture must be greater than about 3×10^{-4} . This means that the ratio of lens diameter to focal length must be greater than .07 or the " f " number smaller than 14. Since, in order to obtain sufficient illumination to properly expose films the f numbers are generally around 1, we shall also ignore the aperture effect of the optical systems.

Figure 7 shows some of the transfer

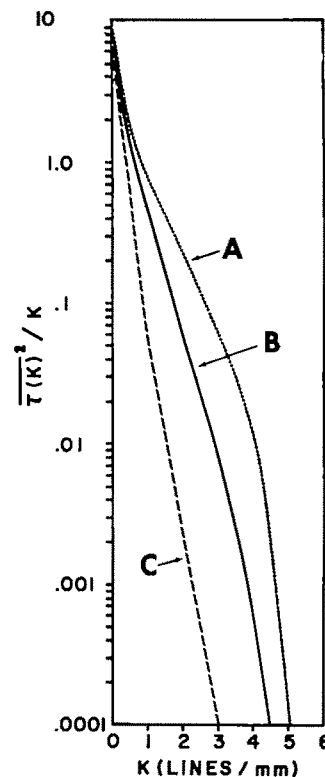


FIG. 7. Data of Figure 6 replotted as $\tau(K)^2/K$ versus K .

function data replotted as $\tau(K)/K$ from which the values of Km and

$$\int_{0.1}^{Km} \log_{10} \frac{\tau(K)^2}{K} dK$$

were obtained as a function of H . From the previous equations, then, the information capacity in bits per sq. mm. can be calculated as a function of H . This is shown for all systems in Figure 8 while Figure 9 shows Km as a function of H . It is obvious from both the graphs that the information capacity and Km increase approximately as $\log H$ over most the range.

Regarding the values of H , it is obvious that this is the product of a constant, the incident photon flux, and the gain of the over-all system as calculated by Equation 3 from the data in Table 1. For the average flux incident upon the detector during a radiologic examination, we shall use 2.8×10^6 photons/mm.²/mr. For σ , measure-

ments¹² have shown this to be about 3 without a grid and $\frac{1}{2}$ with a grid, and we shall use the latter value in all the calculations. For the special case of laminagraphy, the out-of-focus layers increase the over-all background density which may be considered to be an increase in σ since these photons do not contribute to the information. A value of $\sigma = 30$ will be assumed typical of laminagrams. We shall also assume the same modulation transfer function for the in-focus-layer as for a finite spot x-ray tube with screened film recognizing, that this is certainly worse in practice since the "nearly in focus" layers would tend to blur or spread out any image.

Concerning viewing by the eye, we are really interested in the information capac-

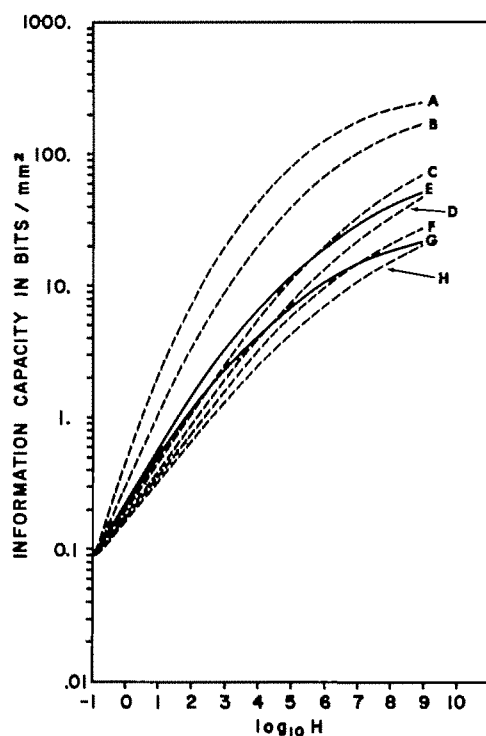


FIG. 8. Information capacity as a function of $\log H$ for a 2 mm. focal spot combined with (A) film, (B) film plus intensifying screen, (C) visual fluoroscopic screen and/or image amplifier, (D) image amplifier plus 35 mm. film, (E) image amplifier plus image orthicon, (F) image amplifier plus 16 mm. film and, (G) image amplifier plus 8 mm. film or videcon.

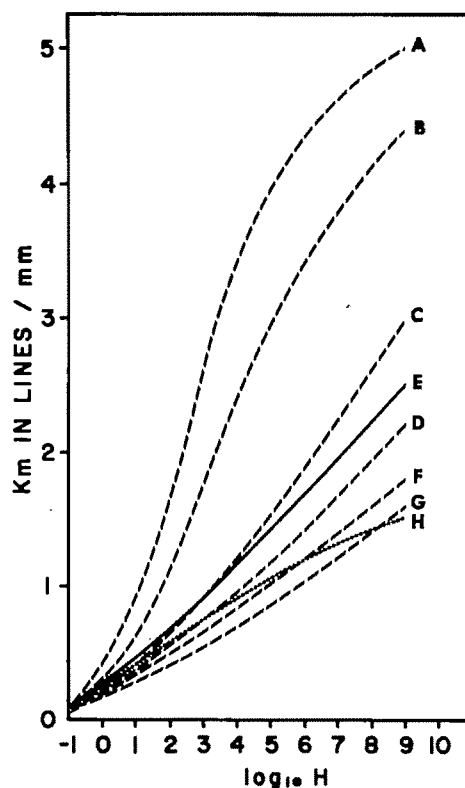


FIG. 9. "Apparent resolution" K_m as a function of $\log H$ for a 2 mm. x-ray focal spot combined with (A) film, (B) film plus intensifying screen, (C) visual fluoroscopic screen and/or image amplifier, (D) image amplifier and 35 mm. film, (E) image amplifier and image orthicon, (F) image amplifier and 16 mm. film, (G) image amplifier and 8 mm. film, and (H) image amplifier and videcon.

ity of the final image on the retina and not that of the eye-brain system. However, for a proper comparison of systems, we must account for the "storage" or "integration" time of the eye since this will determine the total number of photons involved in each picture element just like the exposure time for film. Rose¹⁹ has concluded that the storage time of the eye is about 0.2 seconds and that the threshold signal to noise ratio for observing single areas in a luminous field varies between 3 and 5. On the other hand, Morgan¹⁸ has deduced a threshold signal to noise ratio of 0.3 based on noise equivalent pass bands ranging from 0.13 to 0.04 seconds obtained from flicker-fusion data and spatial pass bands obtained from

sinusoidal bar patterns. This latter value of threshold signal to noise ratio means that the eye could perceive an area that differs in photon count by less than one-half the *rms* variations in equivalent areas in the surrounds—a phenomenally low value that would raise serious statistical questions regarding the validity of any one such observation. A simple explanation is, of course, that the test patterns used in Morgan's analysis are repeated regularly in both space and time and the eye can perform a spatial autocorrelation of these signals and hence use both an apparently lower signal to noise ratio and shorter storage time. This would be quite similar to the operation of the "Computer of Average Transients (CAT)" which is based on the fact that the amplitudes of repeated signals add linearly while that of noise does not. Since in this paper we shall be concerned with noncorrelated signals, we shall use a storage time of 0.2 sec. The time required to scan a complete picture would, of course, be greater than this, which illustrates the value of permanent storage (*i.e.*, film) for casual re-examination without increasing the exposure dose.

Regarding the effect of the true modulation transfer function of the eye (not the sine-wave response which includes the whole eye—brain system), we note that only the pupillary lens and scatter in the eye fluids are of concern. Since the cut-off frequency of an ideal lens is about 300 lines per mm. on the retina,²¹ which corresponds to about 20 lines per mm. on a real object at 25 cm. viewing distance and which is much larger than the resolution possible with a finite x-ray spot, we shall ignore the transfer function of the eye. It is to be noticed that if we introduce a magnifying lens to view even a true size object (*i.e.*, the image on a direct view fluorescent screen), we will increase the viewing aperture of the eye and hence better the signal to noise ratio as explained previously. However, too much magnification forces the eye to examine the details of each resolvable element and lowers the signal to noise ratio by changing

the area over which spatial integration occurs. This is quite similar to looking at a radiograph with a microscope where the eye sees a mass of detail but loses all ability to create an interpretable image. It is quite illustrative to view a radial bar pattern on a direct view fluorescent screen with a low power magnifying lens. A perceptible increase in detail will be noticed until the magnification becomes too large. For the purposes here, we shall include the aperture effect of the eye but ignore its modulation transfer function.

RESULTS AND DISCUSSION

A condensation of all calculations for particular assumed conditions is shown in Table II. The columns labeled Km° and $(I)^\circ$ are for the image just prior to the first detection where $G=1$ and represent the maximum apparent resolution and capacity available. It is to be emphasized that these are calculated for a 2 mm. x-ray focal spot and a target skin distance of 100 cm. Reduction to a 1 mm. spot or doubling the target skin distance can increase these figures for film (and film plus screen) by a factor ranging between 2 and 4 but do little for fluoroscopy and image amplifiers under the conditions shown. The very small figures for image amplifiers are due, for the most part, to the very low exposures stipulated and, of course, the very low initial absorption coefficients. Casually, it would appear that image amplifiers could be improved by thickening the front converter layer since the transfer function is mostly controlled by the electron optics and final output phosphor.

It is also to be noticed that the figure for visual fluoroscopy does not take into account the sine wave response of the eye-brain system at low light levels.²¹ The figure listed assumes that the observer is using a lens that improves the poor resolution of the dark adapted eye at these low levels to, at least, match that of the screen. Under these conditions, the eye could perceive detail equivalent to that enumerated but would take a much longer time to scan

TABLE II

System	Gain	Dose at Detector (mr)	H	K _m (lines/ mm.)	(I) ^o (bits/ mm. ²)	K _m (lines/ mm.)	(I) (bits/ mm. ²)
Unscreened Film	1/34	75	2.1×10^6	4.8	210	4.5	140
Screened Film	1/2.5	5	1.7×10^5	4.2	100	3.1	43
Visual Fluorography	1/125	0.2 (0.2 sec.) 2.0	136 1,360	3.6 4.1	50 120	0.7 1.0	1.4 2.8
9 Inch Image Amplifier Fluoroscopy	1/21.4	0.1 (0.2 sec.) 1.0	400 4,000	3.4 3.9	40 75	0.8 1.4	2.0 4
9 Inch Image Amplifier Recorded on							
a) 8 mm. Film	1/20	0.1 (per frame)	430	3.4	44	0.5	1.0
b) 16 mm. Film	1/20	0.1	430	3.4	44	0.65	1.3
c) 35 mm. Film	1/20	0.1	430	3.4	44	0.7	1.5
d) Videcon	1/20	0.1	430	3.4	44	0.7	1.7
e) Orthicon	1/20	0.1	430	3.4	44	0.8	2.5
Laminagraphy	1/2.5	5	6,840	3.2	30	2.6	17
Television							0.6×10^8 per frame
Film Alone							10^6

the whole image and perceive large organ contours.

Relative to the orthicon, the lower figure for the videcon is due entirely to its smaller front converter screen. These two figures for capacity refer to the electrical signal output but in terms of equivalent area of object rather than electrical bandwidth, since the two are obviously related. For a 4.5 mc. bandwidth and a 30 db. signal to noise ratio, the television electrical line alone can accommodate about 10^6 bits per frame which drops to about 0.6×10^6 bits per frame when projected on a typical kinescope with equal horizontal and vertical resolution. This means essentially that one television frame (two interlaced pictures and 4.5 mc. bandwidth) can handle the information contained in about 60 cm. $\times$ 60 cm. of a field viewed by an image amplifier-videcon chain and about 10 cm. $\times$ 10 cm. of a field viewed by screened film. It is impor-

tant to note that repeating the frames (about 6 times during the 0.2 sec. storage time of the eye) will increase the capacity in the last case since such repetition will increase H . It is also to be noted that one cannot directly add the total information in superposed frames because of redundancy—one can only consider the change in signal to noise ratio by the superposition of identical signals in the presence of noise. In the case of viewing stationary objects, it would obviously be of advantage to have a kinescope phosphor with a time constant longer than that of the eye to provide a longer integration time and, hence, an even larger signal to noise ratio.

In discussing television, it is worthwhile to remember that the conventional process of scanning by moving the cathode ray spot continuously in the horizontal direction and stepwise in the vertical is really a one dimensional presentation in the sense that

the only time axis is the horizontal axis. Besides the electrical bandwidth limitation, one has further degradation by the modulation transfer function of the spot alone in the horizontal direction and the spot plus the scan steps in the vertical. Also, any mathematical operation (*i.e.*, differentiation for contour enhancement) will show only in the horizontal direction. *Y* axis modulation will eliminate the apparent line structure but not change any of the above considerations.

To properly present a two dimensional picture with a one dimensional system, one must scan in both directions along both axes of any orthogonal coordinate system with unequal scan frequencies. Under these circumstances, then, not only can one perform simple mathematical operations (such as contour enhancement and aperture correction) but also one can approach the resolution limit of the two dimensional modulation transfer function of the recording spot alone. These considerations are of particular importance in mechanical scintiscanning systems where a large variety of spot sizes, shapes, and *y* axis modulations have been introduced to make the pattern appearance more pleasing to the eye but with inevitable degradation of the over-all transfer function.

Some investigators have stressed the use of one large spot or multiple spot distribution shaped like the viewing collimator. Even if ideal two dimensional scanning were used, it is obvious that in such cases the over-all transfer function would be the square of that of the collimator alone and, hence, represent considerable degradation. At very low signal densities and small spot sizes, however, the eye cannot spatially integrate very well and there may be some advantage in enhancing the ability of the eye to detect a change even at the expense of resolution. Minification might also prove of importance here.

Regarding the reduction of radiographs for more convenient storage (*i.e.*, micro-filming), it is obvious that there again is some degradation due to the minification

and the optics involved. Since the exposure light may be made as bright as desired, we may neglect the aperture effect; however, the change in the modulation transfer function must be taken into account. A $\times 20$ reduction (*i.e.*, a 14×17 inch film to 35 mm. film) will change the transfer function of the recording film such that its *K* value at .01 is about 10 lines/mm. This would have little effect (about a 10 per cent reduction in capacity and *Km*) for the 2 mm. focal spot radiograph with either screened film or plain film. However, if a 1 mm. spot is used or a larger target skin distance, the degradation could be on the order of 50 per cent for both factors.

While more exact data will change the above listed absolute values when they become available, it is felt that any changes will be reasonably small. Most important are the relative values for all systems and the degradation from input to output caused by each system and each element in each system.

It is fairly obvious that the information capacity of any system may be determined more easily and exactly merely by measuring the over-all modulation transfer function and the final signal to noise ratio under the usual operating conditions. Concerning such a determination, it is most important to remember that the signal should be the original x-ray beam for the typical operating conditions of intensity and storage time and the transfer function should be determined by placing the known grating at the position of the patient. Although the lack of such data forced the assumptions and calculations contained in this paper, these do illustrate the effect of each element in the system and allow the assessment of any inferior components.

Again, let it be stressed that we are determining the information capacity of a system and not the information content of a message. Only a person with experience can say that one given system provides sufficient information to be of value while another system does not. This is particularly true in dose-limited systems where one

cannot arbitrarily increase the capacity and apparent resolution simply by increasing the exposure.

Regarding diagnoses, it remains that probably far less information is required than is usually present. For example, one can readily identify physical objects and even faces with simple profiles (or contours) that lack shades of gray, and, hence, have a smaller information content. Likewise, the apparent success in aiding diagnoses of contrast enhancement, background erase, etc., which only diminish the capacity of the over-all system, is a further indication of the concept of eliminating "undesired" and confusing information. Thus, one may predict a reasonable reduction in the information capacity required of future systems to produce a given diagnosis provided all the available and necessary information is coded and handled in the most appropriate manner. A similar prediction regarding the lowering of the system capacity requirements might also be made on the basis that lower capacity systems can be made with much shorter access times and possibly less expense to store and re-examine the data—forcing one to choose between perhaps unnecessary information and many more procedures in a given time. To date, we have been limited to coding messages for interpretation by the eye and comparing such against images retained in the memory bank of the brain. Whether or not there are superior, more rapid, and less expensive systems than the eye and eye-brain system—or other methods of optimizing the present system by superior coding techniques—remains to be seen.

Department of Radiology
Western Reserve University
Wearn Laboratory for Medical Research
2064 Abington Road
Cleveland, Ohio 44106

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THE RADIANT ENERGY RECEIVED BY PATIENTS IN DIAGNOSTIC X-RAY PRACTICE*

By RUSSELL H. MORGAN and JUDITH C. GEHRET
BALTIMORE, MARYLAND

THIS paper reports an investigation of the radiant energy projected on and received by patients undergoing x-ray examination in a large teaching hospital. The purposes of this study were (1) to investigate the influence of age and sex on the radiant energy needed for each of the commonly performed x-ray procedures; (2) to determine the manner in which the radiant energy used in diagnostic radiology is distributed according to body region; (3) to evaluate excessive field size as a cause of unnecessary exposure in radiography; and (4) to examine the use of radiant energy data in the estimation of annual genetic dose.

Two factors influenced the decision to undertake this study. First, data on the projected radiant energy levels used in diagnostic practice in the United States have not been available. Second, there was reason to believe that such data might be useful in the delineation of a number of problem areas in radiation protection which require the attention of public health workers.

METHOD OF PROCEDURE

Ten of the radiographic and fluoroscopic rooms of the Johns Hopkins Hospital were equipped with instruments with which the quantity of radiant energy projected on a patient during x-ray study could be measured.⁹ Each instrument consisted of a large, differential-type ionization chamber and a digital readout device (Fig. 1). The walls of the chamber were constructed of polyvinyl chloride. The entrance wall of the upper section and the exit wall of the lower section were 0.8 mm. thick while the thick-

ness of the separating wall was 3.3 mm. The thicker separating wall served as the chamber's compensating filter as well as its sectional barrier. Polyvinyl chloride has a mass attenuation coefficient closely similar to aluminum over a wide range of photon energy. Its density is 1.35. The total filtration of the chamber therefore approached 2.5 mm. Al (density 2.7). Air was used as the chamber gas. The depth of the chamber's upper (entrance) section was 5 mm. and that of the lower (exit) section, 20 mm. The chamber's energy response was uniform ± 10 per cent when the x-ray equipment was operated at 45 kvp. and above.

The ionization chamber, in the case of radiography, was mounted on the patient side of an adjustable collimator, the chamber being sufficiently large to intercept all of the radiation projected on the patient below, regardless of the size of the collima-

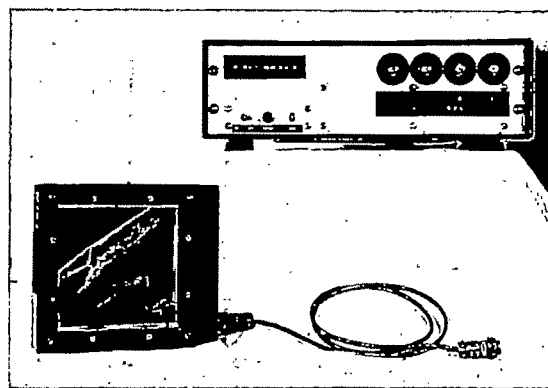


FIG. 1. Instrument for measuring radiant energy projected on patients during radiography and fluoroscopy. Transparent ionization chamber is mounted below collimator of radiographic tube or in front of shutters of fluoroscope.

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From the Department of Radiological Science, The Johns Hopkins University.

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tor opening. Because of the use of polyvinyl chloride, a transparent material, in the chamber's walls, the collimator's field-localizing light beam could be employed in its normal fashion. In the case of fluoroscopy, the chamber was mounted on the patient side of the fluoroscope's adjustable shutters, about 1 inch below the surface of the table top. Again, the chamber was sufficiently large to intercept all of the radiation projected on the patient regardless of the size of the shutter opening. In all cases, the readout device was located adjacent to the x-ray control mechanism where it could be easily observed by the x-ray technologist. Instruments were placed on a broad range of radiographic and fluoroscopic equipment, including apparatus used for such special procedures as angiocardiology and cerebral arteriography. Total beam filtration on all equipment was 3.2 mm. Al.

Radiant energy values were measured in millijoules. It will be recalled that 1 millijoule is equal to 10^4 ergs. Also, the absorption of 10 millijoules of radiant energy represents an integral dose of 1 kilogram-rad.

Data collection was begun late in 1961 and continued through early 1964. During this time, measurements were made on more than 36,000 patients.

In the case of radiography, measurements of radiant energy were made and recorded for each film or portion of a film exposed. In the case of fluoroscopy, measurements were made of the total radiant energy, including that delivered during spot-filming, recorded on the instrument at the end of a fluoroscopic examination.

In addition to the radiant energy measurements, data were also recorded on the age, sex, height and weight of each patient examined. One data card was completed for each examination performed. When a patient was subjected to two or more examinations, an additional data card was completed for each examination. However, when it was necessary for technical reasons to repeat an examination, a new data card was not initiated. Instead, the new radiant

energy data were added to those previously recorded. The results of the study, therefore, reflect the influence of repeated examinations due to technical error on unnecessary patient exposure.

RESULTS OF THE STUDY

Over the 2 year period of study, a sufficient number of patients was examined to permit 10 or more readings on each of almost all of the 30 most commonly performed radiographic and fluoroscopic procedures in each of 10 age groups and in each of the sexes. The mean values of these measurements are recorded in Tables IA and IB. In each case, the data indicate the total radiant energy required for all films exposed during the examination. In the few instances where gaps occur in the data, less than 10 readings were taken and, hence, no entry has been made.

It will be observed that the radiant energy projected on a patient increases substantially for any given examination type as one proceeds from childhood to adulthood. This, of course, is what one might expect. It will also be observed that by far the largest amounts of radiant energy are delivered in those examinations pertaining to the abdomen. Again, this is to be expected since the thickness of the trunk is such that considerably more radiant energy is absorbed in the abdomen than in such other body parts as the extremities and the skull. It is noteworthy that although the chest is usually of approximately the same thickness as the abdomen, considerably smaller amounts of radiant energy were measured in chest radiography than in radiography of the abdomen. The radiolucency of the lungs accounts for this difference. Finally, it will be noted that when an examination includes fluoroscopy, a substantial fraction of the total radiant energy projected on the patient is due to the fluoroscopic portion of the procedure.

Although the data presented in Tables IA and IB are in themselves of interest from several points of view, their relative importance can be evaluated only after

TABLE I A
MEAN PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION (MALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull	13.6	24.2	31.8	69.8	75.4	93.6	77.5	83.9	82.0	68.5
Sinuses	9.3	18.0	24.1	38.4	61.1	56.2	49.7	58.2	60.7	44.7
Mastoids		26.0	32.8	43.0	70.0	45.2	60.4			
Facial Bones	15.9	16.6	43.2	43.1	37.6	64.8	58.5	60.7		
Mandible				48.4	36.1	34.7	25.6	33.1	29.3	28.0
Cervical Spine	6.7	11.7	28.7	31.5	38.4	48.8	53.5	52.5	49.3	38.7
Chest	4.5	5.8	12.0	28.6	47.1	59.2	62.9	62.4	62.2	55.1
Chest with Barium	8.0	4.7	14.2	8.3	43.8			154.5		
Chest Fluoroscopy										
Fluoroscopy			167.9	180.5	199.7	258.9	286.9	304.9	250.8	382.9
Radiography			85.8	81.6	112.4	121.5	131.5	136.7	139.8	124.3
Total			253.7	262.1	312.1	380.4	428.4	441.6	390.6	507.2
Ribs					57.9	50.5	61.4	99.4	82.5	
Thoracic Spine		11.2	23.2	96.6	129.3	99.6	127.2	128.6	138.7	112.2
Gastrointestinal Series										
Fluoroscopy			330.1	295.1	361.4	359.3	346.3	370.1	416.6	397.5
Radiography			115.7	117.0	155.4	182.9	190.4	181.8	195.7	185.2
Total			445.8	412.1	516.8	542.2	536.7	551.9	614.3	582.7
Gallbladder					148.0	122.3	129.5	96.3	162.4	219.8
Small Bowel Series					245.6	210.9	128.6	121.8	197.0	
Barium Enema										
Fluoroscopy			115.0	211.1	262.4	230.5	236.0	254.7	262.2	269.7
Radiography			145.0	299.1	256.4	329.9	391.6	361.3	364.8	331.1
Total			260.0	510.2	518.8	560.4	627.6	626.0	627.0	600.8
Pyelogram (intravenous)	20.3	43.3	122.8	317.4	484.3	457.7	519.2	509.3	536.8	450.7
Abdomen	6.2	11.0	33.6	45.7	76.3	79.3	93.7	103.3	109.9	94.0
Lumbar Spine	3.8	16.7	42.8	112.6	207.1	293.1	350.1	296.5	373.6	317.9
Pelvis	4.6	6.0	11.8	16.3	29.3	53.9	80.3	72.5	86.2	75.5
Shoulder	2.6	3.4	12.8	10.6	28.3	24.6	22.4	23.4	16.2	19.5
Elbow	3.9	4.2	6.1	14.5	5.8	9.0	9.6	13.9	12.3	
Forearm	11.3	5.3	7.3	8.7		5.8	5.8			
Wrist		10.6	7.8	11.9	13.3	12.3	10.3	14.9		
Hand	4.6	3.3	5.8	7.4	10.6	10.6	9.6	11.2	14.6	20.0
Hip	5.3	12.8	49.8			86.4		71.9	63.1	65.6
Femur	4.0	5.1	18.0				32.3	23.3	46.7	21.8
Knee	4.2	4.2	4.4	4.8	7.2	8.1	8.0	7.9	13.5	14.3
Lower Leg	5.9	18.9	15.1	6.7	20.7		11.0	8.3	19.7	
Ankle	4.3	9.9	7.3	5.6	13.1	10.9	15.9	12.3	8.8	
Foot	2.5	5.1	10.1	13.2	14.4	20.7	13.5	18.5	49.0	19.5

weight is given to the probabilities with which each of the examinations is performed. An examination, seldom done, may be expected to be of little importance even when it involves the use of relatively large amounts of radiant energy. On the other hand, a frequently performed procedure might be responsible for a substantial fraction of the radiation received by patients,

even though the energy used per examination is small.

In Tables IIA and IIB are listed the probabilities, based on the experience of the Johns Hopkins Hospital, with which each of the several examinations, shown in Tables IA and IB, is performed. In general, these values are not dissimilar to those reported by others.^{2,4} The values for skull examina-

TABLE I B
MEAN PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION (FEMALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull	13.4	17.7	35.4	54.6	77.1	77.3	67.0	63.6	72.5	70.0
Sinuses	10.2	13.6	23.8	47.4	63.2	51.6	48.2	45.3	44.4	38.5
Mastoids	8.0	28.9	34.3	58.6		64.0	39.4	65.8	41.8	
Facial Bones		14.5			43.2	68.9	45.1			
Mandible					46.0	17.6	31.2	36.1		
Cervical Spine	7.5	12.5	17.2	27.0	27.8	36.2	44.7	52.0	75.5	43.0
Chest	4.4	6.6	11.8	23.6	31.1	34.0	41.8	42.8	46.3	37.4
Chest with Barium	5.0	7.0	9.8	13.3	9.5	91.8		109.8		
Chest Fluoroscopy										
Fluoroscopy			141.8	217.7	230.8	291.5	316.6	295.0	259.3	251.8
Radiography			55.5	89.6	90.0	111.8	113.5	119.0	115.8	90.2
Total			197.3	307.3	320.8	403.3	430.1	414.0	375.1	342.0
Ribs				46.5	78.3	47.7	73.5	64.9	70.6	49.0
Thoracic Spine			16.4	29.3	71.9	107.5	85.1	107.8	109.8	83.5
Gastrointestinal Series										
Fluoroscopy			272.4	415.9	418.7	381.4	354.3	376.4	402.0	396.2
Radiography			102.5	146.5	156.6	163.5	176.5	173.6	180.2	159.2
Total			374.9	562.4	575.3	544.9	530.8	550.0	582.2	555.4
Gallbladder					54.3	109.7	118.9	127.3	89.9	72.7
Small Bowel Series				49.0		119.7	141.7	121.3	116.7	121.5
Barium Enema										
Fluoroscopy			115.0	224.2	215.4	199.6	252.3	235.1	283.3	264.5
Radiography			169.6	246.8	285.7	270.7	317.2	319.7	324.1	322.2
Total			284.6	471.0	501.1	470.3	569.5	554.8	607.4	586.7
Pyelogram (intravenous)	18.2	41.8	161.7	264.5	317.7	415.4	519.0	489.7	517.0	447.2
Abdomen	5.6	10.1	21.2	63.9	72.8	82.7	88.1	97.8	115.5	81.6
Lumbar Spine	4.9	19.6	37.4	206.0	196.9	293.1	249.7	232.5	227.3	220.3
Pelvis	2.7	7.7	8.6	72.5	80.1	72.8	63.2	54.3	78.3	63.5
Shoulder	3.2	3.3	6.1	6.8	16.4	18.2	14.9	21.9	17.9	20.4
Elbow	6.2	5.0	5.4		10.3	8.7	6.9	12.1	5.0	
Forearm	5.0	3.0		13.0			11.4	20.2		
Wrist	1.3	3.6	6.5	6.1	10.9	11.7	6.7	6.9	20.2	
Hand	1.6	3.9	9.9	8.7	10.6	15.6	10.4	13.6	9.6	18.0
Hip	4.9	9.7				99.0	117.3	74.2	67.5	63.0
Femur	1.3				32.8	40.0	39.5	21.2	23.6	21.0
Knee	2.7	4.9	4.4	12.3	7.3	11.0	22.8	11.9	20.8	14.5
Lower Leg	1.8	7.8		9.4	10.6	30.1	24.6	14.7	7.6	
Ankle	2.8	5.8	6.1	7.8	16.3	11.7	8.4	12.2		10.2
Foot	2.2	6.9	7.8	17.0	13.5	21.0	14.8	21.8	12.0	22.2

tions in children are somewhat higher at this hospital than elsewhere. However, for other examinations, probability differences are generally of a minor character.

The relative contribution of any one examination type to the total radiation administered to patients in diagnostic radiology is shown in Tables IIIA and IIIB where, for each examination type, age

group and sex, are tabulated the products of the radiant energy data of Tables IA and IB by the probability data of Tables IIA and IIB.

It will be observed that the chest examination in all age groups constitutes one of the most important procedures from the standpoint of its contribution to the total radiant energy projected on the patient. Al-

though the chest examination, itself, does not result in the delivery of large amounts of radiant energy, the probability of such an examination being done is so great that when considered in relation to the total number of examinations performed, this procedure contributes a relatively large percentage of the total radiant energy delivered. It will also be noted that several other examinations of the trunk, particularly the gastrointestinal series, the barium enema study and intravenous pyelography contribute substantially to projected radiant energy values. Indeed, these three procedures together with the chest examination are responsible for more than half of all of the radiant energy delivered to patients undergoing diagnostic x-ray study.

Of some interest are the totals listed for each age group at the bottom of Tables

IIIA and IIIB. These energy values represent the average radiant energy projected on a patient when he or she is examined. For example, a male in the 20-29 age group, *on average*, intercepts approximately 80 millijoules of radiant energy from the x-ray tube when he is subjected to a single diagnostic x-ray procedure.

The examination types in the foregoing tables include the great majority of procedures undertaken in radiologic facilities in the United States. Of the remainder, most contribute relatively small amounts of additional radiation. There are, however, a small number of special procedures which, even though they are relatively infrequently performed, result in the delivery of substantial amounts of radiant energy to the patient. These are the procedures listed in Tables IVA and IVB. The data presented in these tables indicate the probabil-

TABLE II A
PROBABILITY OF EXAMINATION BEING PERFORMED (MALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull	0.1180	0.1166	0.0974	0.0695	0.0624	0.0536	0.0535	0.0424	0.0422	0.0427
Sinuses	0.0073	0.0209	0.0284	0.0201	0.0205	0.0194	0.0175	0.0183	0.0127	0.0095
Mastoids		0.0086	0.0137	0.0050	0.0044	0.0035	0.0037			
Facial Bones	0.0071	0.0168	0.0127	0.0184	0.0179	0.0105	0.0105	0.0068		
Mandible				0.0042	0.0062	0.0040	0.0034	0.0023	0.0020	0.0013
Cervical Spine	0.0086	0.0136	0.0093	0.0172	0.0212	0.0287	0.0310	0.0306	0.0212	0.0146
Chest	0.5873	0.3908	0.3339	0.4272	0.4052	0.4108	0.4188	0.4344	0.4573	0.4544
Chest with Barium	0.0273	0.0266	0.0194	0.0080	0.0042			0.0026		
Chest Fluoroscopy			0.0060	0.0088	0.0068	0.0109	0.0147	0.0143	0.0117	0.0115
Ribs					0.0077	0.0091	0.0056	0.0050	0.0049	
Thoracic Spine		0.0022	0.0073	0.0088	0.0090	0.0114	0.0108	0.0104	0.0081	0.0079
Gastrointestinal Series			0.0120	0.0109	0.0300	0.0500	0.0561	0.0639	0.0654	0.0588
Gallbladder					0.0057	0.0114	0.0225	0.0202	0.0221	0.0161
Small Bowel Series					0.0022	0.0038	0.0022	0.0022	0.0036	
Barium Enema			0.0057	0.0067	0.0086	0.0198	0.0258	0.0353	0.0404	0.0450
Pyelogram (intravenous)	0.0203	0.0301	0.0227	0.0188	0.0258	0.0351	0.0390	0.0513	0.0607	0.0805
Abdomen	0.0338	0.0311	0.0224	0.0385	0.0575	0.0639	0.0609	0.0507	0.0647	0.0757
Lumbar Spine	0.0075	0.0060	0.0123	0.0151	0.0289	0.0441	0.0365	0.0329	0.0261	0.0189
Pelvis	0.0122	0.0143	0.0163	0.0176	0.0187	0.0138	0.0145	0.0173	0.0178	0.0289
Shoulder	0.0041	0.0092	0.0140	0.0188	0.0157	0.0116	0.0125	0.0095	0.0105	0.0095
Elbow	0.0045	0.0285	0.0187	0.0167	0.0110	0.0078	0.0067	0.0041	0.0020	
Forearm	0.0120	0.0456	0.0484	0.0105		0.0096	0.0048			
Wrist		0.0193	0.0414	0.0268	0.0183	0.0056	0.0063	0.0076		
Hand	0.0144	0.0330	0.0394	0.0611	0.0448	0.0341	0.0180	0.0137	0.0096	0.0061
Hip	0.0054	0.0079	0.0090			0.0053		0.0054	0.0037	0.0095
Femur	0.0050	0.0203	0.0160				0.0059	0.0022	0.0018	0.0061
Knee	0.0094	0.0219	0.0370	0.0339	0.0249	0.0180	0.0136	0.0146	0.0078	0.0110
Lower Leg	0.0123	0.0216	0.0184	0.0130	0.0148		0.0109	0.0073	0.0054	
Ankle	0.0031	0.0098	0.0287	0.0289	0.0306	0.0209	0.0142	0.0095	0.0041	
Foot	0.0119	0.0228	0.0320	0.0213	0.0302	0.0145	0.0153	0.0096	0.0078	0.0095
Total	0.9114	0.9176	0.9223	0.9255	0.9331	0.9313	0.9351	0.9240	0.9131	0.9174

TABLE II B
PROBABILITY OF EXAMINATION BEING PERFORMED (FEMALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull	0.1027	0.0970	0.0795	0.0475	0.0481	0.0468	0.0379	0.0351	0.0467	0.0414
Sinuses	0.0075	0.0220	0.0215	0.0193	0.0261	0.0225	0.0219	0.0208	0.0152	0.0095
Mastoids	0.0055	0.0156	0.0080	0.0040		0.0031	0.0037	0.0039	0.0026	
Facial Bones		0.0112			0.0090	0.0076	0.0046			
Mandible					0.0043	0.0022	0.0033	0.0016		
Cervical Spine	0.0055	0.0116	0.0136	0.0166	0.0251	0.0276	0.0366	0.0312	0.0218	0.0141
Chest	0.5835	0.4125	0.4156	0.5220	0.4551	0.4130	0.3965	0.3869	0.3918	0.4232
Chest with Barium	0.0353	0.0288	0.0257	0.0099	0.0031	0.0023		0.0013		
Chest Fluoroscopy			0.0051	0.0099	0.0108	0.0106	0.0132	0.0134	0.0089	0.0097
Ribs				0.0067	0.0058	0.0049	0.0048	0.0060	0.0037	0.0051
Thoracic Spine			0.0112	0.0076	0.0058	0.0072	0.0104	0.0129	0.0126	0.0104
Gastrointestinal Series			0.0061	0.0135	0.0233	0.0422	0.0465	0.0560	0.0622	0.0539
Gallbladder					0.0166	0.0272	0.0323	0.0338	0.0343	0.0278
Small Bowel Series				0.0031		0.0033	0.0021	0.0011	0.0042	0.0046
Barium Enema			0.0056	0.0103	0.0114	0.0243	0.0350	0.0360	0.0486	0.0542
Pyelogram (intravenous)	0.0209	0.0375	0.0355	0.0229	0.0352	0.0508	0.0550	0.0536	0.0447	0.0370
Abdomen	0.0288	0.0248	0.0323	0.0543	0.0802	0.0674	0.0603	0.0599	0.0641	0.0757
Lumbar Spine	0.0089	0.0080	0.0168	0.0202	0.0254	0.0331	0.0401	0.0363	0.0352	0.0257
Pelvis	0.0183	0.0224	0.0136	0.0139	0.0130	0.0151	0.0173	0.0220	0.0280	0.0384
Shoulder	0.0055	0.0036	0.0061	0.0144	0.0092	0.0111	0.0142	0.0134	0.0180	0.0107
Elbow	0.0022	0.0112	0.0108		0.0092	0.0050	0.0057	0.0060	0.0044	
Forearm	0.0185	0.0351		0.0036			0.0058	0.0048		
Wrist	0.0061	0.0212	0.0215	0.0157	0.0112	0.0088	0.0095	0.0117	0.0119	
Hand	0.0142	0.0284	0.0374	0.0327	0.0249	0.0221	0.0190	0.0171	0.0145	0.0088
Hip	0.0144	0.0044				0.0043	0.0035	0.0052	0.0075	0.0139
Femur	0.0045				0.0013	0.0022	0.0033	0.0031	0.0040	0.0044
Knee	0.0095	0.0160	0.0351	0.0309	0.0151	0.0140	0.0141	0.0181	0.0203	0.0185
Lower Leg	0.0126	0.0208		0.0081	0.0078	0.0084	0.0096	0.0065	0.0066	
Ankle	0.0063	0.0140	0.0257	0.0202	0.0233	0.0185	0.0150	0.0185		0.0076
Foot	0.0085	0.0224	0.0262	0.0224	0.0216	0.0178	0.0135	0.0153	0.0124	0.0125
Total	0.9192	0.8682	0.8527	0.9296	0.9216	0.9235	0.9344	0.9315	0.9213	0.9072

ity with which the several examination types may be performed, tabulated again according to age group and sex, in the experience of this hospital.

The examination types listed in Tables IVA and IVB are performed sufficiently seldom that it was not possible to obtain mean projected radiant energy values per examination for each age group and for the two sexes. Instead, it was necessary to combine the data of both sexes and to restrict the age groupings to children of ages 0-14 and adults of ages 15-99. The resultant values are listed in Table V. The relative importance of these data is shown in Tables VIA and VIB where, for each examination type, age group and sex are listed the products of the radiant energy data of Table V by the probability data of Tables IVA and IVB.

It will be observed that although each of

the examination types is performed rather infrequently, the contribution of several to the total quantity of radiant energy projected on patients is substantial. This is due to the relatively large number of films which are characteristically obtained in some cases (*e.g.*, angiocardiology); in other cases, fluoroscopy contributes substantially.

In Tables VIIA and VIIB, the data of Tables IIIA and IIIB and of Tables VIA and VIB are combined and tabulated according to body region. Such a tabulation permits an evaluation of the distribution of radiant energy throughout the body from one age group to another. It will be seen that in childhood most of the radiation is delivered to the head, neck and thorax. Only small amounts are administered to the abdomen and extremities. After the patient reaches the age of 10 years, the dis-

tribution shifts rapidly so that by the age of 20 years, most of the radiant energy is directed toward the abdomen with only small amounts directed toward the head and neck. The trend continues throughout adulthood with the preponderance of abdominal radiation becoming increasingly marked at the upper age levels.

TABLE III A

PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION, WEIGHTED ACCORDING TO THE LIKELIHOOD THAT THE EXAMINATION IS PERFORMED (MALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull	1.60	2.82	3.10	4.85	4.70	5.02	4.14	3.55	3.46	2.92
Sinuses	0.07	0.38	0.68	0.77	1.25	1.09	0.87	1.07	0.77	0.42
Mastoids		0.22	0.45	0.22	0.31	0.16	0.22			
Facial Bones	0.11	0.28	0.55	0.79	0.67	0.68	0.62	0.41		
Mandible				0.20	0.22	0.14	0.09	0.08	0.06	0.04
Cervical Spine	0.06	0.16	0.27	0.54	0.81	1.40	1.66	1.61	1.05	0.56
Chest	2.64	2.27	4.01	12.22	19.08	24.32	26.34	27.10	28.44	25.04
Chest with Barium	0.22	0.13	0.27	0.07	0.18			0.40		
Chest Fluoroscopy										
Fluoroscopy			1.01	1.58	1.36	2.83	4.37	4.37	2.93	4.41
Radiography			0.51	0.72	0.77	1.32	1.94	1.96	1.63	1.43
Total			1.52	2.30	2.13	4.15	6.31	6.33	4.56	5.84
Ribs					0.45	0.46	0.34	0.50	0.40	
Thoracic Spine		0.02	0.17	0.85	1.17	1.14	1.37	1.33	1.12	0.89
Gastrointestinal Series										
Fluoroscopy			3.96	3.21	10.83	17.94	19.43	23.63	27.35	23.38
Radiography			1.39	1.27	4.66	9.14	10.69	11.61	12.79	10.89
Total			5.35	4.48	15.49	27.08	30.12	35.24	40.14	34.27
Gallbladder					0.85	1.40	2.91	1.95	3.58	3.54
Small Bowel Series					0.54	0.80	0.29	0.27	0.70	
Barium Enema										
Fluoroscopy			0.65	1.41	2.25	4.57	6.09	9.35	10.59	12.14
Radiography			0.82	2.00	2.21	6.53	10.11	12.76	14.73	14.90
Total			1.47	3.41	4.46	11.10	16.20	22.11	25.32	27.04
Pyelogram (intravenous)	0.41	1.30	2.79	5.98	12.49	16.04	20.25	26.14	32.56	36.30
Abdomen	0.21	0.34	0.75	1.76	4.39	5.07	5.71	5.24	7.11	7.11
Lumbar Spine	0.03	0.10	0.53	1.70	5.98	12.93	12.77	9.75	9.75	6.01
Pelvis	0.06	0.09	0.19	0.29	0.55	0.74	1.16	1.25	1.54	2.18
Shoulder	0.01	0.03	0.18	0.20	0.44	0.29	0.28	0.22	0.17	0.18
Elbow	0.02	0.12	0.11	0.24	0.06	0.07	0.06	0.06	0.02	
Forearm	0.14	0.24	0.35	0.09		0.06	0.03			
Wrist		0.20	0.32	0.32	0.24	0.07	0.06	0.11		
Hand	0.07	0.11	0.23	0.45	0.47	0.36	0.17	0.15	0.14	0.12
Hip	0.03	0.10	0.45			0.46		0.39	0.24	0.62
Femur	0.02	0.10	0.29				0.19	0.05	0.08	0.13
Knee	0.04	0.09	0.16	0.16	0.18	0.15	0.11	0.12	0.11	0.16
Lower Leg	0.07	0.41	0.28	0.09	0.31		0.12	0.06	0.11	
Ankle	0.01	0.10	0.21	0.16	0.40	0.23	0.23	0.12	0.04	
Foot	0.03	0.12	0.32	0.28	0.43	0.30	0.21	0.18	0.38	0.18
Totals										
Fluoroscopy			5.62	6.20	14.44	25.34	29.89	37.35	40.87	39.93
Radiography	5.84	9.73	19.39	36.22	63.85	90.36	102.93	108.42	120.98	113.64
Total	5.84	9.73	25.01	42.42	78.29	115.70	132.82	145.77	161.85	153.57

UNNECESSARY PATIENT EXPOSURE

One of the principal causes of unnecessary exposure in diagnostic radiology is the use of excessive field size. Excessive exposure

rates and exposure times do not usually constitute a problem in radiography because such excesses lead without exception to films of poor quality. Hence, most phy-

TABLE III B

PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION, WEIGHTED ACCORDING TO THE LIKELIHOOD THAT THE EXAMINATION IS PERFORMED (FEMALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull	1.38	1.72	2.81	2.60	3.71	3.62	2.54	2.23	3.38	2.90
Sinuses	0.08	0.30	0.51	0.91	1.65	1.16	1.06	0.94	0.67	0.37
Mastoids	0.04	0.45	0.27	0.24		0.20	0.15	0.26	0.11	
Facial Bones		0.16			0.39	0.52	0.21			
Mandible					0.20	0.04	0.10	0.06		
Cervical Spine	0.04	0.14	0.23	0.45	0.70	1.00	1.64	1.62	1.65	0.61
Chest	2.57	2.72	4.90	12.32	14.15	14.04	16.57	16.56	18.14	15.83
Chest with Barium	0.18	0.20	0.25	0.13	0.03	0.21		0.15		
Chest Fluoroscopy										
Fluoroscopy			0.72	2.15	2.50	3.09	4.19	3.96	2.31	2.44
Radiography			0.29	0.88	0.97	1.18	1.50	1.60	1.03	0.88
Total			1.01	3.03	3.47	4.27	5.69	5.56	3.34	3.32
Ribs				0.31	0.45	0.23	0.35	0.39	0.26	0.25
Thoracic Spine			0.18	0.22	0.41	0.77	0.88	1.39	1.38	0.87
Gastrointestinal Series										
Fluoroscopy			1.66	5.59	9.74	16.11	16.46	21.08	25.01	21.37
Radiography			0.62	1.97	3.64	6.90	8.20	9.72	11.21	8.59
Total			2.28	7.56	13.38	23.01	24.66	30.80	36.22	29.96
Gallbladder					0.90	2.98	3.83	4.31	3.08	2.02
Small Bowel Series				0.15		0.39	0.29	0.13	0.49	0.56
Barium Enema										
Fluoroscopy			0.65	2.32	2.44	4.85	8.83	8.46	13.77	14.33
Radiography			0.95	2.54	3.25	6.58	11.11	11.51	15.74	17.45
Total			1.60	4.86	5.69	11.43	19.94	19.97	29.51	31.78
Pyelogram (intravenous)	0.38	1.57	5.75	6.05	11.17	21.09	28.54	26.24	23.13	16.56
Abdomen	0.16	0.25	0.68	3.47	5.84	5.57	5.31	5.86	7.41	6.18
Lumbar Spine	0.04	0.16	0.64	4.16	5.00	9.71	10.01	8.43	7.39	5.66
Pelvis	0.05	0.17	0.12	1.01	1.04	1.10	1.10	1.20	2.19	2.44
Shoulder	0.02	0.01	0.04	0.10	0.15	0.20	0.21	0.29	0.32	0.22
Elbow	0.01	0.06	0.06		0.09	0.04	0.04	0.07	0.02	
Forearm	0.09	0.11		0.05			0.07	0.10		
Wrist	0.01	0.08	0.14	0.10	0.12	0.10	0.06	0.08	0.24	
Hand	0.02	0.11	0.37	0.28	0.26	0.35	0.20	0.23	0.14	0.16
Hip	0.07	0.04				0.43	0.41	0.39	0.51	0.88
Femur	0.01				0.04	0.09	0.13	0.07	0.09	0.09
Knee	0.03	0.08	0.15	0.38	0.11	0.15	0.32	0.22	0.42	0.27
Lower Leg	0.02	0.16		0.08	0.08	0.25	0.24	0.09	0.05	
Ankle	0.02	0.08	0.16	0.16	0.38	0.22	0.13	0.22		0.08
Foot	0.02	0.15	0.20	0.38	0.29	0.37	0.20	0.33	0.15	0.28
Totals										
Fluoroscopy			3.03	10.06	14.68	24.05	29.48	33.50	41.09	38.14
Radiography	5.23	8.73	19.34	38.93	55.05	79.51	95.39	94.68	99.20	83.13
Total	5.23	8.73	22.37	48.99	69.73	103.56	124.87	128.18	140.29	121.27

TABLE IV A
PROBABILITY OF EXAMINATION BEING PERFORMED (MALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull Laminagram	0.0003	0.0006	0.0007	0.0021	0.0018	0.0022	0.0017	0.0010	0.0013	0.0005
Cerebral Arteriogram	0.0016	0.0013	0.0030	0.0029	0.0027	0.0060	0.0049	0.0103	0.0054	0.0010
Cervical Myelogram		0.0003	0.0003	0.0004	0.0002	0.0013	0.0015	0.0009	0.0003	0.0005
Bronchogram		0.0003	0.0003	0.0013	0.0002	0.0020	0.0015	0.0022	0.0016	0.0008
Angiocardiogram	0.0021	0.0010	0.0020	0.0021	0.0015	0.0002	0.0001		0.0003	
Thoracic Arteriogram	0.0003	0.0003			0.0004	0.0007	0.0008	0.0031	0.0016	0.0015
Abdominal Arteriogram	0.0005	0.0006	0.0007	0.0008	0.0002	0.0011	0.0020	0.0034	0.0015	0.0005
Lumbar Myelogram	0.0002	0.0009	0.0003	0.0012	0.0022	0.0091	0.0070	0.0047	0.0034	0.0010
Femoral Arteriogram					0.0002	0.0004	0.0018	0.0038	0.0034	0.0018
	0.0050	0.0050	0.0073	0.0108	0.0094	0.0230	0.0213	0.0294	0.0188	0.0056

TABLE IV B
PROBABILITY OF EXAMINATION BEING PERFORMED (FEMALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull Laminagram	0.0002	0.0012	0.0014	0.0009	0.0009	0.0010	0.0010	0.0008	0.0007	0.0007
Cerebral Arteriogram	0.0016	0.0048	0.0037	0.0022	0.0047	0.0053	0.0048	0.0048	0.0044	0.0023
Cervical Myelogram			0.0005	0.0009	0.0004	0.0011	0.0005	0.0011	0.0005	
Bronchogram	0.0006	0.0012	0.0009	0.0009	0.0005	0.0019	0.0013	0.0018	0.0009	0.0007
Angiocardiogram	0.0018	0.0004	0.0033	0.0031	0.0002	0.0001	0.0001	0.0001		
Thoracic Arteriogram	0.0002		0.0005		0.0004	0.0001	0.0006	0.0011	0.0009	0.0012
Abdominal Arteriogram	0.0004		0.0014		0.0013	0.0008	0.0004	0.0005	0.0009	0.0007
Lumbar Myelogram	0.0012	0.0004	0.0005	0.0009	0.0022	0.0041	0.0037	0.0020	0.0018	0.0009
Femoral Arteriogram		0.0004			0.0004	0.0007	0.0011	0.0004	0.0005	0.0028
	0.0060	0.0084	0.0122	0.0089	0.0110	0.0151	0.0115	0.0126	0.0106	0.0097

sicians and technologists take considerable care to use exposure factors which, for the film or film-screen combination being exposed and for the film processing conditions at hand, yield a film whose densities fall within the useful range of film blackening.

To estimate the extent to which excessive field size is a problem in radiography, calculations were made of the mean projected radiant energy per examination which should have been measured for each of the examination types listed in Tables IA and IB if, for the film-screen combination in use, proper x-ray tube potentials and currents, exposure times, field sizes and target-film distances had been used. These calculations were made with the assistance of the data plotted in Figure 2, which shows the relationship between peak x-ray tube

potential and the radiant energy per milli-ampere-second, projected by the tube on a field, 1 square inch in cross section, at a distance of 36 inches. These data apply to

TABLE V
MEAN PROJECTED RADIANT ENERGY IN MILLIJOULES
PER EXAMINATION (MALES AND FEMALES)

Type of Examination	Age Group	
	0-4	15-99
Skull Laminagram	82.5	252.5
Cerebral Arteriogram	113.5	369.5
Cervical Myelogram	118.0	362.0
Bronchogram	97.0	394.0
Angiocardiogram	648.0	2735.0
Thoracic and Abdominal Arteriogram	302.0	1207.0
Lumbar Myelogram	140.0	542.0
Femoral Arteriogram	93.6	276.0

TABLE VI A

PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION, WEIGHTED ACCORDING
TO THE LIKELIHOOD THAT THE EXAMINATION IS PERFORMED (MALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull Laminogram	0.0248	0.0495	0.0578	0.5302	0.4545	0.5555	0.4292	0.2525	0.3282	0.1262
Cerebral Arteriogram	0.1816	0.1476	0.3405	1.0716	0.9976	2.2170	1.8106	3.8058	1.9953	0.3695
Cervical Myelogram			0.0354	0.1448	0.0724	0.4706	0.5430	0.3258	0.1086	0.1810
Bronchogram		0.0291	0.0291	0.5122	0.0788	0.7880	0.5910	0.8668	0.6304	0.3152
Angiocardiogram	1.3608	0.6480	1.2960	5.7435	4.1025	0.5470	0.2735		0.8205	
Thoracic Arteriogram	0.0906	0.0906			0.4826	0.8449	0.9656	3.8005	1.9208	1.8105
Abdominal Arteriogram	0.1510	0.1812	0.2114	0.9656	0.2413	1.3277	2.4140	4.0450	1.8209	0.6035
Lumbar Myelogram	0.0280	0.1260	0.0420	0.6504	1.1924	4.9322	3.7940	2.5474	1.8428	0.5420
Femoral Arteriogram					0.0552	0.1104	0.4968	1.0488	0.9384	0.4968
	1.8368	1.2720	2.0122	9.6183	7.6776	11.7933	11.3177	16.6926	10.4059	4.4447

TABLE VI B

PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION, WEIGHTED ACCORDING
TO THE LIKELIHOOD THAT THE EXAMINATION IS PERFORMED (FEMALES)

Type of Examination	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Skull Laminogram	0.0165	0.0990	0.1155	0.2272	0.2272	0.2525	0.2525	0.2020	0.1768	0.1768
Cerebral Arteriogram	0.1816	0.5448	0.4200	0.8129	1.7366	1.9584	1.7736	1.7736	1.6258	0.8498
Cervical Myelogram			0.0590	0.3258	0.1448	0.3982	0.1810	0.3982	0.1810	
Bronchogram	0.0582	0.1164	0.0873	0.3546	0.1970	0.7486	0.5122	0.7092	0.3546	0.2758
Angiocardiogram	1.1664	0.2592	2.1384	8.4785	0.5470	0.2735	0.2735	0.2735		
Thoracic Arteriogram	0.0604		0.1510		0.4828	0.1207	0.7242	1.3277	1.0863	1.4484
Abdominal Arteriogram	0.1208		0.4228		1.5691	0.9656	0.4828	0.6035	1.0863	0.8449
Lumbar Myelogram	0.1680	0.0560	0.0700	0.4878	1.1924	2.2222	2.0054	1.0840	0.9756	0.4878
Femoral Arteriogram		0.0374			0.1104	0.1932	0.3036	0.1104	0.1380	0.7728
	1.7719	1.1128	3.4640	10.6868	6.2073	7.1329	6.5088	6.4821	5.6244	4.8563

TABLE VII A

RADIANT ENERGY IN MILLIJOULES PROJECTED PER AVERAGE EXAMINATION:
DATA OF TABLES III A AND VI A GROUPED ACCORDING TO BODY REGION

Body Region	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Head and Neck	2.05	4.06	5.48	9.12	9.48	11.73	10.38	11.10	7.77	4.62
Thorax	4.31	3.19	7.29	21.70	27.67	32.25	36.19	40.33	37.89	33.90
Abdomen	0.89	2.14	11.33	19.24	46.18	81.42	95.62	108.54	124.36	117.60
Upper Extremity	0.24	0.70	1.19	1.30	1.21	0.85	0.60	0.54	0.33	0.30
Lower Extremity	0.20	0.92	1.71	0.69	1.38	1.25	1.36	1.97	1.90	1.59
Total	7.69	11.01	27.00	52.05	85.92	127.50	144.15	162.48	172.25	158.01

TABLE VII B

RADIANT ENERGY IN MILLIJOULES PROJECTED PER AVERAGE EXAMINATION:
DATA OF TABLES III B AND VI B GROUPED ACCORDING TO BODY REGION

Body Region	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Head and Neck	1.74	3.41	4.42	5.57	8.76	9.15	7.91	7.48	7.79	4.91
Thorax	4.04	3.40	8.72	24.84	19.75	20.66	25.00	26.36	24.56	21.99
Abdomen	0.92	2.21	11.56	27.75	45.78	78.47	96.17	98.63	111.48	96.49
Upper Extremity	0.15	0.37	0.61	0.53	0.62	0.69	0.58	0.77	0.72	0.38
Lower Extremity	0.17	0.55	0.51	1.00	1.01	1.70	1.73	1.43	1.36	2.37
Total	7.02	9.94	25.82	59.69	75.92	110.67	131.39	134.67	145.91	126.14

conditions where a 4 valve, full-wave rectified x-ray generator is used with a total beam filtration of 3.2 mm. Al, the conditions which prevailed on all of the x-ray equipment used in this study.

The values of field size, used in these calculations, were those which were just sufficient to cover the dimensions of the films recommended for use by the exposure charts regularly used by the x-ray technologists of the hospital. Proper kilovoltage and milliamperes-second values were determined from the same charts in accordance with average patient thickness data listed in Tables VIIIA and VIIIB. These data were derived from an anthropometric study, conducted in this laboratory, of 1,500 hospital patients, male and female, whose ages ranged from 10 months to 78 years. A detailed report of this investigation will be given in a future publication.

The ratios of the measured-to-calculated projected radiant energy values for the several examination types are listed in Table IX. The data for both sexes have been grouped and values have been divided into two age categories, one for children of 0-14 years of age and one for adults of 15-99 years of age. Values of certain examinations were sufficiently similar that additional groupings were also made. For example, all of the upper extremity values were combined as were also those for the lower extremity.

If no unnecessary exposure were delivered to patients, the values in Table IX would be equal to 1.0 or less. As will be seen, however, values greater than this are frequently encountered. Of special note are the values for chest examinations. Particularly in the adult, the amount of unnecessary exposure is quite substantial and raises a question as to its cause. With little question, the difficulty stems from the fact that chest films usually are exposed at a

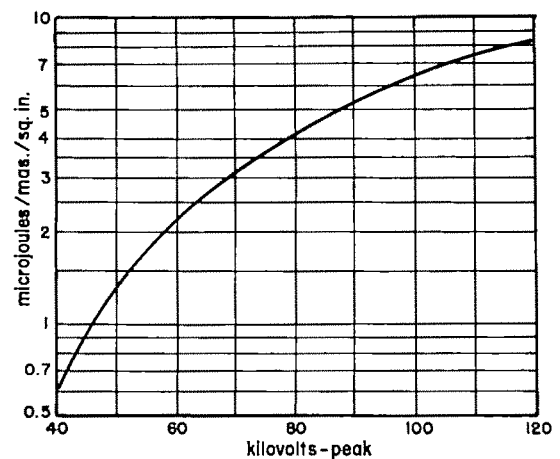


FIG. 2. Relationship between radiographic tube potential and radiant energy in microjoules per milliamperes-second projected on a field 1 sq. inch in cross section at a target-field distance of 36 inches. Data are for a 4 valve, full-wave rectified generator operating at tube currents from 50 to 300 ma. and for a total beam filtration (inherent + added filter) of 3.2 mm. Al.

TABLE VIII A
AVERAGE ANTHROPOMETRIC CHARACTERISTICS OF PATIENTS
UNDERGOING RADIOLOGIC EXAMINATION (MALES)

	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Weight (kg.)	12.3	24.9	43.1	60.8	68.9	72.1	72.5	71.6	70.7	68.0
Height (cm.)	82	123	150	169	173	173	173	172	171	169
Thickness of Head (cm.)	16.8	18.3	18.7	19.0	19.6	19.6	19.6	19.6	19.6	19.0
Width of Head (cm.)	12.6	13.5	14.3	14.8	15.1	15.1	15.1	15.1	15.1	14.8
Thickness of Thorax (cm.)	13.4	15.4	18.6	20.8	22.4	22.8	23.4	23.4	22.8	22.4
Width of Thorax (cm.)	17.1	22.6	26.8	30.0	31.5	32.0	32.5	32.5	32.0	31.5
Abdominal Thickness (cm.)	12.4	14.6	18.2	20.9	22.5	23.1	23.2	23.0	22.8	22.4
Abdominal Width (cm.)	15.5	19.1	24.7	28.4	29.5	30.6	30.7	30.5	30.1	29.6
Xiphoid-to-Pubic Symphysis Distance (cm.)	22	29	34	38	39	39	39	39	38	38
Abdominal Volume (10 ³ cc.)	3.3	6.4	12.0	17.7	20.3	21.6	21.8	21.4	20.5	19.7

tube-film distance of 72 inches whereas most other procedures are carried out with a distance of 36 inches. It appears that technologists in the performance of chest procedures tend to be careless in adjusting the collimator to its proper dimensions. If the collimator has been set for a 14×17 inch film exposed at a tube-film distance of 36 inches, it is not infrequently left in this position when the distance is changed for chest radiography.

The problem of chest radiography was recognized early in the study. However, its

correction was not vigorously attacked until sufficient data were collected to demonstrate the problem's magnitude. It is perhaps of some interest to report that the problem is correctable by educational methods. However, continuous vigilance must be maintained because technologists who tend to be careless are likely to become wayward soon after educational pressures have been removed.

It will be observed from Table IX that in the remaining examinations, unnecessary exposure is not generally high. Indeed, in

TABLE VIII B
AVERAGE ANTHROPOMETRIC CHARACTERISTICS OF PATIENTS
UNDERGOING RADIOLOGIC EXAMINATION (FEMALES)

	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Weight (kg.)	12.0	25.3	44.5	55.0	60.0	61.4	63.8	64.3	64.3	60.0
Height (cm.)	81.8	123	151	161	163	162	162	161	161	160
Thickness of Head (cm.)	16.6	18.5	18.7	19.0	19.2	19.2	19.3	19.3	19.3	19.0
Width of Head (cm.)	12.4	13.7	14.3	14.8	14.8	14.8	14.8	14.8	14.8	14.8
Thickness of Thorax (cm.)	13.2	15.6	18.6	20.0	21.0	21.2	21.5	21.5	21.5	21.0
Width of Thorax (cm.)	17.0	22.9	26.8	29.1	30.0	30.3	30.6	30.6	30.6	30.0
Abdominal Thickness (cm.)	12.2	14.8	18.3	19.7	20.7	21.0	21.3	21.5	21.5	20.7
Abdominal Width (cm.)	15.2	19.4	24.7	27.3	28.1	28.4	28.8	28.9	28.9	28.1
Xiphoid-to-Pubic Symphysis Distance (cm.)	22	29	34	36	37	37	37	36	36	35
Abdominal Volume (10 ³ cc.)	3.2	6.5	12.1	15.1	16.9	17.3	17.8	17.6	17.6	16.2

TABLE IX
RATIOS OF MEASURED-TO-OPTIMIZED
PROJECTED RADIANT ENERGY

Type of Examination	Age Group	
	Children	Adults
Skull	0.57	0.94
Sinuses	0.37	0.49
Cervical Spine	1.60	1.82
Chest	2.26	3.24
Thoracic Spine	—	0.75
Gastrointestinal Series (Radiographic)	1.17	1.21
Gallbladder	—	1.05
Barium Enema	—	1.23
Intravenous Pyelogram	0.89	1.34
Abdomen	0.92	1.48
Lumbar Spine	0.71	1.17
Pelvis	0.75	1.34
Upper Extremity	1.14	1.02
Lower Extremity	0.85	0.80

the case of some procedures (e.g., the head), the ratio of measured-to-calculated projected radiant energy is less than 1.0, indicating that field sizes smaller than those needed to cover the film in use have been employed. This perhaps should not be surprising since it is well known that these examinations are usually conducted with small-field collimation in which the irradiated field is restricted to dimensions substantially less than those of the film. Indeed, if such collimation is not employed, film quality deteriorates.

It is noteworthy that substantially less unnecessary exposure is employed in children than in adults at this hospital. This

can be ascribed to a small but diligent group of technologists in the Pediatric Division.

It perhaps should also be pointed out that all values listed in Table IX are exaggerated because of examinations repeated for technical reasons of one sort or another. The number of these repeated examinations amounts to approximately 10 per cent of the total procedures performed. Therefore, if it were possible to eliminate such examinations, the values in Table IX would be reduced accordingly.

The data presented in Table IX permit the calculation of the projected radiant energy which would prevail in diagnostic practice if the use of excessive field sizes and repeated examinations were eliminated in radiography. Tables XA and XB give the totals of these optimized calculations for each age group and sex, determined from the radiographic components of the data presented in Tables IIIA and IIIB after the data have been divided by appropriate ratios given in Table IX, if these ratios exceeded a value of 1.0. Also included is a listing of the totals of the measured radiant energy data due to radiography from Tables IIIA and IIIB.

The ratios of optimized-to-measured values of radiant energy indicate the magnitude of the unnecessary exposure from the use of excessive field size and from repeated examinations prevailing in this hospital. As will be seen from Tables XA and XB, the unnecessary exposure in the adult amounts to somewhat over 30 per cent on average. In children, levels of unnecessary

TABLE X A
AVERAGE PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION:
OPTIMIZED AND MEASURED DATA (MALES)

	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Optimized	4.21	8.15	16.31	24.08	41.95	62.08	70.21	74.52	81.13	76.28
Measured	5.84	9.73	19.39	36.22	63.85	90.36	102.93	108.42	120.98	113.64
Ratio of O/M	0.72	0.84	0.84	0.67	0.66	0.69	0.68	0.69	0.67	0.67

TABLE X B
AVERAGE PROJECTED RADIANT ENERGY IN MILLIJOULES PER EXAMINATION:
OPTIMIZED AND MEASURED DATA (FEMALES)

	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Optimized	3.69	7.00	15.84	24.94	36.90	56.68	68.27	66.93	69.90	57.99
Measured	5.23	8.73	19.34	38.93	55.05	79.51	95.39	94.68	99.20	83.13
Ratio of O/M	0.71	0.81	0.82	0.64	0.67	0.71	0.72	0.72	0.70	0.70

exposure are smaller (*i.e.*, ratios of optimized-to-measured values of radiant energy are larger). As previously pointed out, this is due to the exercise of greater care by the pediatric technologists.

ANNUAL GENETIC DOSE

Increasing awareness of the genetic effects of ionizing radiation and the rapid growth of clinical radiology have combined to arouse in recent years considerable interest in the gonad dose or genetically significant annual dose received from diagnostic x-ray examinations. Several studies have been published in which these doses have been estimated for a number of countries.^{3,6,7,8,11}

From a public health standpoint, a single measurement of annual genetic dose is of limited usefulness. Of greater value is a series of measurements, taken over a period of time, indicating the trend of dosage levels. From such data, the impact of changes in professional and technical practice and the benefits of protective measures introduced to reduce patient exposure may be determined. Unfortunately, rigorously scientific methods of measuring annual genetic dose are too laborious to permit their use on a continuing basis. There is, therefore, a need for a simpler method which may be conveniently used even though it may provide less precise data.

The annual genetic dose received by a population may be calculated from the following formula⁶:

$$G = \frac{\sum D_{ij} P_{ij} N_{ij}}{\sum P_{ij} N_{ij}}, \quad (1)$$

where D_{ij} , P_{ij} and N_{ij} are the average annual gonad dose, the average child expectancy and the number of individuals, respectively, in the i th age group and j th sex of the population under study. Data on average child expectancy and population statistics are generally available. Hence, the development of a simplified method of calculating annual genetic dose depends on one's finding an easy way to estimate gonad dose.

The gonad dose of a population such as that of the United States, may be estimated from measurement of projected radiant energy, as given in previous sections of this paper, if the following 3 assumptions are made: (1) gonad dose is proportional to the average absorbed dose of the abdomen; (2) the techniques of diagnostic radiology used in large medical centers are similar to those employed throughout the nation as a whole; and (3) the age and sex distributions of the persons undergoing x-ray studies at large medical centers are similar to those of the total x-rayed population. Although the validity of each of these assumptions is difficult to verify, none seems unreasonable. Current radiographic and fluoroscopic techniques involve the use of radiation projected from a multiplicity of directions, centered on a large number of target areas and involving a variety of field sizes. This complexity of procedure when integrated over the total of all examinations leads to conditions which favor a simple relationship between gonad dose and average abdominal dose.

Comprehensive data on the radiologic techniques employed by various profes-

TABLE XI
AVERAGE ABDOMINAL DOSE IN MILLIRADS PER EXAMINATION

Sex	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Males	13	16	46	52	108	177	208	241	288	286
Females	14	16	45	87	128	205	257	266	301	282

sional groups within the country are not available. However, a recent study of the processing techniques used in radiography indicates that the techniques of this medical center are quite similar to those employed by the local medical profession as a whole.¹⁰

Comment has been made previously on the similarity of the age and sex distributions of the persons undergoing x-ray study at this hospital and elsewhere in the United States. As indicated, differences in these distributions are small.

The radiation received by the abdomen in diagnostic radiology is almost exclusively due to those examinations in which the useful beam is projected directly on the abdomen. Although some radiation is received from other body regions by scattering processes, its amount is relatively small. Therefore, the average absorbed dose per examination received by the abdominal tissues *from all examinations* may be calculated from projected radiant energy data in accordance with the following formula:

$$\bar{D}_a' = a[\Sigma E_k p_k] / V\rho \times 10^2, \quad (2)$$

where E_k is the radiant energy in millijoules projected on the abdomen when an examination of type k is performed, p_k is the probability with which this examination is performed, a is the fraction of the projected radiant energy absorbed by the abdominal tissues, V is the abdominal volume in cm.³ and ρ is the abdominal density. It will be recognized that this formula simply states that the average absorbed dose received by the abdominal tissues per examination is equal to the radiant energy projected on and absorbed by these tissues, per exam

ination, divided by the weight of the abdomen. The numerical term in the equation is introduced to yield dosage values in rads.

Values of $\bar{D}_a'$, calculated from the experience of this hospital, are listed according to age and sex in Table XI. These data have been derived from values of $\Sigma E_k p_k$ in Tables VIIA and VIIB. In these calculations, values of abdominal volume were taken from Tables VIIIA and VIIB, determined from the formula:

$$V = (\pi/4)bcd, \quad (3)$$

where b is the distance between the xiphoid process and symphysis pubis, c is the thickness of the abdomen at the iliac crests and d is the width of the abdomen also at the iliac crests. A value of 1.05 was used for abdominal density. A value of 0.5 was employed as the fraction of projected energy absorbed. Although the value of this parameter may vary through wide limits, depending on the anthropometric characteristics of the individual under examination and the photon energy of the exposing radiation, recent work by Carlsson¹ indicates that a value of 0.5 is not likely to be substantially in error, on average.

When a population of N people receives a total of n x-ray examinations per year, the annual abdominal dose per individual, $\bar{D}_a$, is equal to the abdominal dose per examination multiplied by the ratio, n/N ; that is,

$$\bar{D}_a = \bar{D}_a' n / N. \quad (4)$$

Also, if the annual gonad dose, D_g , is proportional to the average abdominal dose per year, then

$$D_g = m\bar{D}_a, \quad (5)$$

TABLE XII
POPULATION STATISTICS OF THE UNITED STATES IN 1960: NUMBER OF INDIVIDUALS
IN EACH AGE GROUP (IN MILLIONS)

Sex	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Male	10.33	9.50	8.52	6.63	10.61	11.93	11.03	8.86	6.34	4.57
Female	9.99	9.19	8.25	6.59	11.06	12.50	11.45	9.17	7.06	5.73

where m is a proportionality constant. Hence, the annual gonad dose received by the i th age group and the j th sex is given by the formula:

$$D_{gij} = m\bar{D}_{a'ij} \cdot (np_{sij}/N_{ij}), \quad (6)$$

where n is the number of examinations of all types performed per year in the total population and p_{sij} is the probability of an individual, within a population of x-rayed persons, falling in the i th age group and the j th sex.

Values of the estimated annual gonad dose, calculated from equation (6) for each of the sexes and for various age groups, are shown in Table XIV. In these calculations, values of $\bar{D}_{a'ij}$ were taken from Table XI, values of N_{ij} from Table XII and values of p_{sij} from Table XIII. The latter table was prepared from the records of over 100,000 persons studied roentgenographically in this hospital during the period July 1, 1963 to June 30, 1964. The value of n , the annual number of x-ray examinations performed in the United States, was taken as 8.9×10^7 , the latest value reported for the year 1960-1961 by the U. S. Public Health Service.⁴ And, the proportionality constant, m , was assigned a value of 0.75 for females and 1.0

for males. These values were chosen on the basis that the ovaries, being deeply buried within the abdomen, are likely to receive a dose somewhat less than the average abdominal dose whereas the testicles, lying on the surface but peripheral to the abdomen, are likely to receive a dose about equal to the average abdominal dose.

When values of gonad dose, listed in Table XIV, are appropriately combined with population and fertility data (Table XV), the annual genetic dose for the United States may be estimated from equation (1). Such calculations indicate the male component to be 11.9 millirads and the female component to be 8.4 millirads.

It will have been observed that projected radiant energy data for obstetrical examinations were not included in the tables from which values of average abdominal dose were calculated for the female. This is because this hospital performs relatively few such examinations. Hence, a value of 8.4 millirads for the female component of the U. S. annual genetic dose is likely to be low. From studies of Hammer-Jacobsen⁸ and the Adrian Committee,⁸ it appears that approximately 25 per cent of the female component is due to obstetrical pro-

TABLE XIII
PROBABILITY OF AN INDIVIDUAL, WITHIN A POPULATION OF X-RAYED PERSONS,
FALLING IN A GIVEN AGE GROUP

Sex	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Male	.0615	.0314	.0299	.0237	.0453	.0549	.0712	.0779	.0616	.0389
Female	.0492	.0248	.0213	.0221	.0554	.0735	.0830	.0743	.0571	.0430

TABLE XIV
ESTIMATED ANNUAL GONAD DOSE IN MILLIRADS

Sex	Age Group									
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	70-99
Males	3.5	2.4	7.2	8.4	20.7	36.7	60.3	95.4	126	101
Females	2.0	1.4	3.9	9.8	21.6	40.5	63.1	72.9	81.7	71.2

cedures. Therefore, it is estimated that the female component for the United States approaches 11.2 millirads.

Because of the absence of obstetrical energy values in this hospital, no calculation of the fetal component of annual genetic dose has been attempted. Such a calculation, however, follows precisely the same principles as those used to obtain the male and female components and may easily be carried out when obstetrical data are available.

It is not possible to compare the estimates of annual genetic dose derived in this paper with data obtained from more rigorous methods because, to date, such data are not available in the United States. However, comparison is possible with values obtained in the United Kingdom and in Denmark. In the former, the Adrian Committee⁸ obtained values of 4.83 mr for the male component and 5.03 mr for the fe-

male. Danish values⁹ were 8.56 mr and 5.91 mr, respectively.

It will be observed that the estimates made in this paper are about double those reported in the United Kingdom and in Denmark. This, however, is not surprising because approximately twice as many x-ray examinations are performed per person per year in the United States as in these countries; *i.e.*, 0.5 examinations per person per year in the United States⁴ *vs.* 0.26 in the United Kingdom⁸ and 0.24 in Denmark.⁹ Hence, the values obtained in this paper conform well to those which might have been expected from the experience of others.

It appears then that the annual genetic dose may be predicted reasonably well from measurements of projected radiant energy made in large centers. It must be emphasized that because of the assumptions on which the method is based, the resulting data are less precise than those based on more direct measurements. Nevertheless, the method should be of value to those wishing to have a relatively easy means of determining annual genetic dose from year to year.

SUMMARY

In this paper, a study is reported in which the radiant energy projected on more than 36,000 patients undergoing diagnostic x-ray examination at the Johns Hopkins Hospital was measured. These data appear to be quite useful in the evaluation of the levels of unnecessary exposure prevailing in diagnostic radiology, particularly when such unnecessary exposure is due to excessive field size in radiography. Such measure-

TABLE XV
EXPECTED FUTURE NUMBER OF CHILDREN
UNITED STATES, 1963

Age	Male	Female
0-1	3.36	3.21
1-4	3.46	3.28
5-9	3.47	3.30
10-14	3.48	3.30
15-19	3.49	3.31
20-24	3.42	2.93
25-29	2.54	1.78
30-34	1.44	0.86
35-39	0.69	0.33
40-44	0.29	0.08
45-49	0.09	0.004
50-59	0.02	0.00
60+	0.00	0.00

ments may also be used effectively to estimate the annual genetic dose due to diagnostic x-ray methods. The relative ease with which such measurements may be collected permits the study of annual genetic dose on a continuing basis, thereby making possible an evaluation of the trends in this dose arising from an increased application of x-rays in medical practice and from the institution of techniques to reduce patient exposure.

Russell H. Morgan
Department of Radiology
The Johns Hopkins Hospital
Baltimore, Maryland 21205

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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Associate Editors: HARRY HAUSER, M.D., RUSSELL H. MORGAN, M.D., EDWARD B. D. NEUHAUSER, M.D.

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Forty-ninth Annual Meeting: Royal York Hotel, Toronto, Ontario, Canada, May 29-31, 1967.

E D I T O R I A L

THE SIXTY-SEVENTH ANNUAL MEETING OF THE AMERICAN ROENTGEN RAY SOCIETY

THE American Roentgen Ray Society will hold its Sixty-seventh Annual Meeting at the San Francisco Hilton Hotel in San Francisco, California, September 27-30, 1966. Throughout its history, the Society has usually convened in the Middle West or Eastern sections of our country and only two meetings have been held in California. For the first time, San Francisco will be our host city and all preparations point to an outstanding convention.

San Francisco is easily accessible by air, land or sea and the jet age has annihilated distance with several airlines having non-stop flights to San Francisco from major transportation centers in the United States. Even with connecting flights, the trip often can be made in less than half a day. Major railroads from the East and Middle West offer comfort and beautiful scenery across the northern, mid or southern sections of our country. For those with plenty of time, ocean travel from the East or Gulf coast areas, via the Panama Canal, would provide a memorable trip to San Francisco.

As a part of New Spain, our convention city was founded in 1776, came under the American flag in 1846, experienced the drama of the Gold Rush of 1849 and 1850s and grew rapidly following completion, in 1869, of the first transcontinental railroad. Growth in size and importance was stopped by a disastrous earthquake on April 18, 1906. Nine years later the Panama-Pacific International Exposition was San Francisco's way of showing the world that the city was completely rebuilt. From that time, growth has been orderly and progressive to the present population of about 800,000. The city's geographic area is hemmed in by

the Pacific Ocean to the West and San Francisco Bay to the East, with nine counties in the Bay Area having a total population of approximately 4,000,000. From San Francisco one may cross the Golden Gate Bridge in a northerly direction to some of the world-famous Redwood Country or he may travel East across the long double-decked Bay Bridge to Oakland. Going South, down the peninsula, the roads lead to San Jose and the California Mainland.

The first-time visitor to San Francisco is always impressed by the many steep hills, Fisherman's Wharf, the Embarcadero, Chinatown, North Beach, Japantown and Ghiradelli Square. The hills are easily conquered by taxi or cablecar and a stroll along Fisherman's Wharf enables one to observe the home-base operations of a fleet of small fishing boats, while the large ocean-going vessels are seen along the Embarcadero. Chinatown, the largest settlement of its kind outside of Asia, is but a short walk from the hotel and the other ethnically orientated sections of the city are easily accessible. North Beach has about 55,000 San Franciscans of Italian extraction while Japantown has about 10,000 of Japanese descent. Restaurants and shops in these areas are characteristic of the country of origin.

San Francisco's roller coaster cablecars not only provide a thrilling ride but afford a practical way of seeing many of the interesting areas in town. In 1869, Andrew Hallidie, a London born engineer and wire rope manufacturer, felt sorry for the teams of horses which struggled violently to haul horse cars up and down the steep San Francisco hills. He devised the cablecar

system and by 1880, one hundred and twelve miles of cables were laid beneath San Francisco streets. Since that time the cablecars have waxed and waned in popularity but in 1964 the system was officially named as a historical monument by the U. S. Interior Department's National Park Service and the city charter now provides that the 3 existing cablecar lines are a permanent part of the city. From a downtown power station, $10\frac{1}{2}$ miles of heavy steel cable goes out at a steady $9\frac{1}{2}$ miles per hour just beneath the street surface of the cablecar routes and returns in an endless loop to the power station for continuous application of force. Street cars have their motormen, buses have their drivers but cablecars have their "gripmen."

By operating a lever, he closes a pincer-like "grip" on the endless cable beneath the car and thus obtains the motive power. While the rides may be thrilling and breathtaking, safety is assured by 4 separate braking devices.

Members and guests will find that the San Francisco Hilton Hotel is new, has excellent facilities for a medical convention and is close to San Francisco's famous Union Square with its fashion-center stores and sidewalk fresh-flower stalls. Newcomers to San Francisco should be aware that the climate is not like that of southern California and, for the months of September and October, the temperature will vary from an average high of 68 to a low of 54. Morning and evening fog, rolling in from the sea, is common but seldom persists throughout the day. September and October are not considered rainy months, but a raincoat and lightweight topcoat are indicated. Most visitors find that the weather is definitely on the "cool" side.

Preparations for the annual meeting have been going on for some time and involve a large number of people. The membership is greatly indebted to Dr. James C. Cook, Manager of the Annual Meeting, and Mr. Clifford L. Sherratt, honorary member of the Society, for their knowledge, ability and experience in planning and correlating

the various functions and activities involving the hotel, technical exhibitors and many society affairs. The technical exhibits will be of the usual high quality and Dr. Joseph O. Reed, Chairman of the Scientific Exhibits Committee, forecasts that many will be attracted by the high quality of the displays and presentations.

With the continuing outstanding direction of Dr. Harold O. Peterson and with Dr. Donn G. Mosser as associate director, the Refresher Courses, so characteristic of our annual meeting, again will see many leading authorities presenting scientific material in an informal manner.

The Scientific Program Committee has selected 51 papers for presentation and many related matters have been handled with the aid of our most efficient Secretary, Dr. C. A. Good, and our illustrious Editor, Dr. Traian Leucutia.

In spite of all outside effort, those closely associated with the American Roentgen Ray Society have been well aware that the success of the Annual Meeting was dependent, to a great degree, on the Committee on Local Arrangements. We have been most fortunate in having Dr. Thomas M. Fullenlove and his wife, Sally, head-up a group of 38 people who are doing their utmost to make the San Francisco meeting a memorable one.

The Ladies' Program begins Monday, September 27, with an afternoon sight-seeing tour of the city (the men are welcome). The final stop will be at Ghiradelli Square, with cocktails and dinner at one of San Francisco's famed restaurants, Senor Pico. Tuesday morning the ladies will gather for a Continental Breakfast, following which there will be a conducted tour of the famous stores in the Union Square area. Prior arrangements are made with each store to be visited and the ladies will be treated as special guests. A highlight of the week will be the Wednesday six-hour trip by bus and the ferry-boat "Trade Fair" to Sausalito for lunch, shopping and a trip through Muir Woods, one of California's famous redwood tree areas. A walking tour

of Chinatown is planned for Thursday morning. The ladies are reminded that not only are low heels fashionable, but they are highly recommended for these trips.

Monday is golfing day for the men with low net competition for the historic Willis F. Manges Trophy, and low gross for the Exhibitors' Trophy. The Committee on Local Arrangements promises a great day of golfing with lunch, dinner and evening entertainment at the Olympic Club. There are two excellent eighteen-hole courses and we will play the one near the Pacific Ocean. The other one was used for the U.S. Open this June. If you fly to San Francisco, check with your airline about the very low cost of shipping your clubs. It is hoped that there will be a large turn-out of members and guests for this fun day.

The Scientific Program begins Tuesday morning at 8:30 A.M. with President Medelman calling the meeting to order and introducing Dr. John B. Saunders, Chancellor of the University of California Medical Center, San Francisco, who will give the Address of Welcome. President Medelman assisted by Dr. Herbert M. Stauffer, Chairman of the Executive Council, will then install Dr. Clyde A. Stevenson as the new President of the Society. The Inaugural Address will be followed by 12 papers that morning. Thirteen papers will be presented, beginning at 8:30 A.M., on each of the following mornings through Friday. Visits to the exhibits are encouraged during the early part of each afternoon and the Instruction Courses will begin promptly at 3:00 P.M.

The Caldwell Lecture will be given Tuesday evening at 8:30 P.M. by Dr. J. Arnold Borgen, Head of the Section of Gastroen-

terology at Scott and White Clinic and Director of Medical Education for Scott and White Memorial Hospital, Temple, Texas. Dr. Borgen's presentation will be "Chronic Ulcerative Colitis: Diagnostic and Therapeutic Problems. A Life-long Study." Dr. Borgen has published over 380 papers and authored four books on disease of the colon. He is recognized throughout the world as a foremost expert in this field. His interest in post-graduate medical education at local, state and national levels will be emphasized by the introduction to be given by Dr. F. J. L. Blasingame, Executive Vice-President of the American Medical Association.

Wednesday afternoon at 1:30 P.M. the American College of Radiology will present a program concerning some of the College activities and there will be a question and answer period. This meeting will terminate in time for the Instruction Courses at 3:00 P.M.

The social highlight of the week will be the Annual Banquet on Thursday evening at 7:30 P.M., preceded by a Cocktail Party beginning at 6:30 P.M. During the banquet, the winners of the Scientific Exhibit Awards will be recognized and acclaimed. The Committee on Local Arrangements promises fine food, excellent entertainment and dancing.

The American Roentgen Ray Society feels that the general excellence of the Program and the attractions of San Francisco justify a large attendance, and it is hoped that radiologists, their families and guests have already made plans and reservations for the meeting. The Officers of the Society extend their most cordial invitation to you.

Clyde A. Stevenson, M.D.
President-Elect



PRELIMINARY PROGRAM
SIXTY-SEVENTH ANNUAL MEETING
OF
THE AMERICAN ROENTGEN RAY SOCIETY

September 27-30, 1966

THE SAN FRANCISCO HILTON HOTEL
SAN FRANCISCO, CALIFORNIA

The Sixty-seventh Annual Meeting of the American Roentgen Ray Society will be held in the new San Francisco Hilton Hotel, San Francisco, California, Tuesday through Friday, September 27 to September 30, 1966.

The Executive Council will meet Sunday, September 25, 9:00 A.M. in the Teakwood Room A, Fourth Floor.

On Monday, September 26, the Annual Golf Tournament for members and guests—competing for the Willis F. Manges Trophy and the Exhibitors' Trophy—will be held at the beautiful Olympic Club, followed by the Annual Golf Dinner at 7:30 P.M. at that Club.

The Scientific Sessions will be held in the morning from 8:30 A.M. to 12:30 P.M., Tuesday through Friday in the Continental Parlor 6-7-8-9. The Caldwell Lecture will be given by Dr. J. Arnold Bargen, Head of the Section on Gastroenterology, Scott and White Clinic and Director of Medical Education of the Scott and White Memorial Hospital, Temple, Texas, on Tuesday evening at 8:30 P.M. in the Continental Parlor 6-7-8-9. He will be introduced by Dr. F. J. L. Blasingame, Executive Vice-President of the American Medical Association. At the conclusion of the Lecture, President Stevenson will present to Doctor Bargen the Caldwell Medal, the highest award of the Society.

The Instruction Courses will be held in the afternoon from 3:00 P.M. to 4:30 P.M. on Tuesday, Wednesday and Thursday and from 1:30 P.M. to 3:00 P.M. on Friday. The detailed plan of the Instruction Courses

will be published in the August issue of the JOURNAL.

The Scientific Exhibits will be set up in the South-West and North Corridors. They will open daily at 8:30 A.M. and will close at 8:00 P.M. Tuesday, 9:00 P.M. Wednesday, 7:30 P.M. Thursday and at 12:30 P.M. Friday.

The Technical Exhibits will be located in the Continental Parlor 1-2-3-4-5, and in the East-North and South Corridors. They will open daily at 8:30 P.M. and will close at 5:30 P.M., Tuesday through Thursday. On Friday, they will close at 12:30 P.M.

The Annual Banquet will be held Thursday evening at 7:30 P.M. in the Continental Parlor 6, preceded by a Cocktail Party beginning at 6:30 P.M. in the Continental Parlor 7-8-9.

The Program Committee, under the Chairmanship of President-Elect Clyde Alan Stevenson, has arranged the following program for the Scientific Sessions.

Tuesday, September 27, 1966
Continental Parlor 6-7-8-9

8:30 A.M.

Call to Order, Sixty-seventh Annual Meeting:
John Paul Medelman, M.D., St. Paul, Minnesota, President.

Address of Welcome: John B. deC. M. Saunders, M.B., F.R.C.S. (Edinburgh), M.D., F.A.C.D. Chancellor, University of California Medical Center, San Francisco, California.

Installation of President-Elect, Clyde Alan Stevenson, M.D., Spokane, Washington, by John Paul Medelman, M.D., St. Paul, Minnesota, President, and Herbert M. Stauffer,

M.D., Philadelphia, Pennsylvania, Chairman of the Executive Council.

Presentation of Past President's Book to John Paul Medelman, M.D., by Clyde Alan Stevenson, M.D.

Presidential Address: President Clyde Alan Stevenson, M.D.

9:10 A.M.

Presiding: Clyde Alan Stevenson, M.D.
Spokane, Washington

1. Para-endocrine Syndromes Associated with Carcinoma of the Lung. Robert P. Barden, M.D., Philadelphia, Pa.
2. Percutaneous Transthoracic Needle Biopsy. Harry L. Stein, M.D. (by invitation), New York, N. Y., and John A. Evans, M.D., New York, N. Y.
3. The Thoracic Radiographic Manifestations of the Malignant Lymphomas. John A. Tobin, M.D. (by invitation), Minneapolis, Minn.
4. Asbestosis and Malignancy. N. G. Demy, M.D., Somerville, N. J., and Howard Adler, M.D., Somerville, N. J.
5. The Chest Roentgenogram Following Supraglottic Sub-total Laryngectomy. Tom W. Staple, M.D. (by invitation), St. Louis, Mo., Edward F. Ragsdale, M.D. (by invitation), St. Louis, Mo., and Joseph H. Ogura, M.D. (by invitation), St. Louis, Mo.
6. Pneumothorax and Pneumomediastinum in the Newborn Infant. D. W. MacEwan, M.D. (by invitation), Winnipeg, Man., J. S. Dunbar, M.D., Montreal, P. Q., B. St. John Brown, M.D. (by invitation), Montreal, P. Q., and M. B. Nogrady, M.D. (by invitation), Montreal, P. Q.
7. Vascular Changes in Pulmonary Emphysema. A. Franklin Turner, M.D. (by invitation), Los Angeles, Calif., and George Jacobson, M.D., Los Angeles, Calif.
8. The Lateral Film in Pulmonary Edema. R. E. Steiner, M.D. (by invitation), London, England, and D. C. Gleason, M.D. (by invitation), St. Louis, Mo.
9. Pneumocystis Carinii Pneumonia (Plasma Cell Pneumonia): Roentgenographic, Pathologic and Clinical Correlation. Sydney F. Thomas, M.D., Chico, Calif., Werner Dutz, M.D. (by invitation), Shiraz, Iran, and Ethelyn Khodadad, M.D. (by invitation), Buffalo, N. Y.

10. Radiologic Manifestation of Confirmed Primary Tuberculosis before and during Antimicrobial Treatment. Alfred L. Weber, M.D. (by invitation), Boston, Mass., Kenneth T. Bird, M.D. (by invitation), Boston, Mass., and Murray L. Janower, M.D. (by invitation), Boston, Mass.
11. Review of Logical Analysis Procedures for Roentgen Diagnosis. Lee B. Lusted, M.D., Portland, Ore.
12. Radioisotope Scanning of Extracranial Tumors. F. J. Bonte, M.D., Dallas, Texas, T. S. Curry, III, M.D. (by invitation), Dallas, Texas, R. E. Oelze, B.S. (by invitation), Dallas, Texas, and A. J. Greenberg, M.D. (by invitation), Dallas, Texas.

Tuesday Evening, September 27, 1966
Eight-thirty o'clock

Continental Parlor 6-7-8-9

THE CALDWELL LECTURE

Chronic Ulcerative Colitis: Diagnostic and Therapeutic Problems. A Life Long Study

By

J. Arnold Barger, M.D.

Head of the Section on Gastroenterology,
Scott and White Clinic

and

Director of Medical Education, Scott
and White Memorial Hospital
Temple, Texas

Introduction by F. J. L. Blasingame, M.D.,
Executive Vice-President, American Medical
Association, Chicago, Illinois.

*Presentation of the Caldwell Medal to DOCTOR
BARGER* by President Stevenson.

Wednesday, September 28, 1966
Continental Parlor 6-7-8-9

8:30 A.M.

Presiding: John F. Holt, M.D.
Ann Arbor, Michigan

13. Cine-Cholangiomanometry. Thomas C. Beneventano, M.D. (by invitation), New York, N. Y., Harold G. Jacobson, M.D., New York, N. Y., Elliott S. Hurwitt, M.D. (by invitation), New York, N. Y., and Clarence J. Schein, M.D. (by invitation), New York, N. Y.

14. A Radiologic Approach to the Renal Mass. Richard B. Hoffman, M.D. (by invitation), Los Angeles, Calif., and John M. Riley, M.D. (by invitation), Los Angeles, Calif.
 15. Roentgenologic Evaluation of Bladder Neck Obstruction. Charles E. Shopfner, M.D., Kansas City, Mo.
 16. Contrast-Globulin Precipitation; A Possible Cause of Induced Renal Failure in Patients with Multiple Myeloma Undergoing Intravenous Pyelographic Examination. Elliott C. Lasser, M.D., Pittsburgh, Pa., Joseph Lang, Ph.D. (by invitation), Pittsburgh, Pa., and Z. A. Zawadzki, M.D. (by invitation), Pittsburgh, Pa.
 17. Fibromuscular Dysplasia of the Renal Arteries. Owings W. Kincaid, M.D., Rochester, Minn., George D. Davis, M.D., Rochester, Minn., Franz J. Hallermann, M.D. (by invitation), Rochester, Minn., and James C. Hunt, M.D. (by invitation), Rochester, Minn.
 18. Radiologic Observations on the Fate of Large Pulmonary Emboli. Arnold Chait, M.D. (by invitation), Brooklyn, N. Y., Donald Summers, M.D. (by invitation), Brooklyn, N. Y., Robert J. Rabinowitz, M.D. (by invitation), Brooklyn, N. Y., Skinsaku Matsumoto, M.D. (by invitation), Brooklyn, N. Y., Norman Krasnow, M.D. (by invitation), Brooklyn, N. Y., and Bernard M. Wechsler, M.D. (by invitation), Brooklyn, N. Y.
 19. Pulmonary Embolic Disease—Pulmonary Angiography: A Study of Indications and Diagnostic Criteria with Correlative Animal Experimentation. Earnest J. Ferris, M.D. (by invitation), Boston, Mass., Robert M. Stanzler, M.D. (by invitation), Boston, Mass., Joseph V. Messer, M.D. (by invitation), Boston, Mass., and James A. Rourke, M.D. (by invitation), Boston, Mass.
 20. Correlative Assessment of the Macroalbumin Lung Scan with the Clinical and Radiographic Chest Findings. D. J. Sieniewicz, M.D., Montreal, P.Q., Leonard Rosenthal, M.D. (by invitation), Montreal, P.Q., and Milton J. Herba, M.D. (by invitation), Montreal, P.Q.
 21. Radiodiagnostic Techniques in the Diagnosis of Pulmonary Thromboembolism. William A. Weidner, M.D. (by invitation), Torrance, Calif., Gabriel Wislon, M.D. (by invitation), Torrance, Calif., George V. Taplin, M.D. (by invitation), Torrance, Calif., and Leonard Swanson, M.D. (by invitation), Torrance, Calif.
 22. Radioisotopic Techniques for Evaluation of Pulmonary Disease. Merle K. Loken, Ph.D., M.D. (by invitation), Minneapolis, Minn.
 23. Radioactive Scanning of Superior Mediastinal Masses. Yen Wang, M.D., Pittsburgh, Pa.
 24. The Clinical Applications of the Anger Gamma Camera to Disease of the Thyroid Gland. John D. McAllister, M.D. (by invitation), Pittsburgh, Pa., Gilbert H. Alexander, M.D. (by invitation), Pittsburgh, Pa., Harold E. Goldberg, M.D. (by invitation), Pittsburgh, Pa., and Joseph A. Marasco, Jr., M.D. (by invitation), Pittsburgh, Pa.
 25. Clinical Use of the Spark Imaging Camera in Nuclear Medicine. J. E. Lofstrom, M.D., Royal Oak, Mich., N. H. Horwitz, Ph.D. (by invitation), Royal Oak, Mich., and A. L. Forsaith, M.S. (by invitation), Royal Oak, Mich.
- Wednesday, September 28, 1966*
Continental Parlor 6
- 1:30 P.M.
- Presiding: Clyde Alan Stevenson, M.D.
Spokane, Washington
- Panel: A Report from the American College of Radiology.
- Moderator:* J. E. Miller, M.D., Dallas, Texas.
- Panelists:* Jackson E. Livesay, M.D., Flint, Michigan; Stanley M. Wyman, M.D., Cambridge, Massachusetts; and Antolin Raventos, M.D., Philadelphia, Pennsylvania. Question and Answer Period.
- Thursday, September 29, 1966*
Continental Parlor 6-7-8-9
- 8:30 A.M.
- Presiding: Herbert M. Stauffer, M.D.
Philadelphia, Pennsylvania
26. Biological Basis of Preoperative Radiation Therapy. W. E. Powers, M.D. (by invitation), St. Louis, Mo., Joseph Ogura, M.D. (by invitation), St. Louis, Mo., and Lily Ann Palmer, M.D. (by invitation), St. Louis, Mo.
 27. Skin Sensitivity in Hyperbaric Radiation

- Therapy. Robert G. Parker, M.D. (by invitation), Seattle, Wash., and Peter Wootton, Hon.B.Sc. (by invitation), Seattle, Wash.
28. The Paradox of Breast Cancer. Vincent P. Collins, M.D., Houston, Texas, and Robert M. Adams, B.S. (by invitation), Austin, Texas.
 29. Palliative Irradiation for Bladder Carcinoma. Herbert E. Brizel, M.D. (by invitation), Louisville, Ky., and Ralph M. Scott, M.D., Louisville, Ky.
 30. Carcinoma of the Palatine Tonsil: 131 Cases Treated between 1950 and 1960. Paul W. Scanlon, M.D., Rochester, Minn., Kenneth D. Devine, M.D. (by invitation), Rochester, Minn., Lewis B. Woolner, M.D. (by invitation), Rochester, Minn., and James B. McBean, M.D. (by invitation), Rochester, Minn.
 31. Strabismus Produced by Intracranial Extension of Cancer of the Nasopharynx Can Be Cured with Radiation Therapy. Charles L. Martin, M.D., Dallas, Texas.
 32. Complete Calibration of an X-Ray Machine. Marvin M. D. Williams, Ph.D., Rochester, Minn., Arnold Feldman, Ph.D. (by invitation), Rochester, Minn., and Joseph A. Anderson, B.S. (by invitation), Rochester, Minn.
 33. Vascular Jet Contraction in Angiography. Heratch Doumanian, M.D. (by invitation), Minneapolis, Minn., and Kurt Amplatz, M.D. (by invitation), Minneapolis, Minn.
 34. Ten Years Experience in Celiac Arteriography in the Diagnosis of Pancreatic, Portal and Hepatic Pathology. B. P. Sammons, M.D. (by invitation), Richmond, Va., and M. P. Neal, Jr., M.D. (by invitation), Richmond, Va.
 35. Experience with Postmortem Cerebral Angiography Performed As Routine Procedure of the Autopsy. Gertraud Wollschlaeger, M.D. (by invitation), Columbia, Mo., Paul B. Wollschlaeger, M.D. (by invitation), Columbia, Mo., and Fred Lucas, M.D. (by invitation), Columbia, Mo.
 36. Positive Contrast Demonstration of the Normal Auditory Canal. David F. Reese, M.D. (by invitation), Rochester, Minn., and James Bull, M.D. (by invitation), London, England.
 37. Pseudo Suprasellar Tumors. William Hanaford, M.D., Los Angeles, Calif., and Larry Bilodeau, M.D. (by invitation), Los Angeles, Calif.
 38. The Radiology of the Meningo-Hypophyseal Trunk. Henry W. Pribram, M.D. (by invitation), Iowa City, Iowa, Thomas R. Boulter, M.D. (by invitation), Iowa City, Iowa, and William F. McCormick, M.D. (by invitation), Iowa City, Iowa.

Friday, September 30, 1966
Continental Parlor 6-7-8-9

8:30 A.M.

Presiding: Justin J. Stein, M.D.
 Los Angeles, California

39. The Use of Barium Sulfate Suspension for the Purpose of Making Early Radiologic Diagnoses in Patients Suspected of Having Obstruction of the Small Intestine. Sidney W. Nelson, M.D., Columbus, Ohio, and Anthimos J. Christoforidis (by invitation), Columbus, Ohio.
40. Superficial Spreading Carcinoma of the Stomach. David Bragg, M.D. (by invitation), New York, N. Y., William Seaman, M.D., New York, N. Y., and R. Lattes, M.D. (by invitation), New York, N. Y.
41. The Retained Gastric Antrum. H. Joachim Burhenne, M.D., San Francisco, Calif.
42. Cartridge-loaded Palm-sized Syringe for Gas Contrast Radiography. Marcia Kepler Bilbao, M.D. (by invitation), Portland, Ore., Charles T. Dotter, M.D., Portland, Ore., and Thomas B. Hutchins, IV (by invitation), Portland, Ore.
43. Radiographic and Anatomic Features of Double Outlet Right Ventricle. Franz J. Hallermann, M.D. (by invitation), Rochester, Minn., Owings W. Kincaid, M.D., Rochester, Minn., Donald G. Ritter, M.D. (by invitation), Rochester, Minn., and Jack L. Titus, M.D. (by invitation), Rochester, Minn.
44. The Predictive Value of Volumetric Study of the Left Ventricle. Melvin M. Figley, M.D., Seattle, Wash., Ward Kennedy, M.D. (by invitation), Seattle, Wash., and John R. Blackmon, M.D. (by invitation), Seattle, Wash.
45. Biplane Selective Coronary Arteriography via Percutaneous Transfemoral Approach. William J. Wilson, M.D. (by invitation), Minneapolis, Minn., Gerald B. Lee, M.D.

- (by invitation), Minneapolis, Minn., and Kurt Amplatz, M.D. (by invitation), Minneapolis, Minn.
46. Controlled Exit Catheterization. Charles T. Dotter, M.D., Portland, Ore., Melvin P. Judkins, M.D. (by invitation), Portland, Ore., and Louis H. Frische, M.D. (by invitation), Portland, Ore.
47. The Newborn Skull. Charles N. Chasler, M.D. (by invitation), Pittsburgh, Pa.
48. Amniography for Placental Localization. George T. Wohl, M.D., Philadelphia, Pa., Myron Blumberg, M.D. (by invitation), Philadelphia, Pa., John P. Emich, M.D. (by invitation), Philadelphia, Pa., Richard W. Schwarz, M.D. (by invitation), Philadelphia, Pa., and Samuel Wiltchik, M.D. (by invitation), Philadelphia, Pa.
49. Intravenous Placentography. Charles K. Hendrick, M.D. (by invitation), Galveston, Texas, and Melvyn H. Schreiber, M.D. (by invitation), Galveston, Texas.
50. Sexual Precocity, Precocious Puberty and Virilism: Radiologic Findings. Herman Grossman, M.D. (by invitation), New York City, N. Y., and Maria New, M.D. (by invitation), New York City, N. Y.
51. A Roentgen Evaluation of Patients with the Turner's Phenotype. David H. Baker, M.D., New York City, N. Y., Walter E. Berdon, M.D. (by invitation), New York City, N. Y., Akira Morishima, M.D. (by invitation), New York City, N. Y. and San Francisco, Calif., and Felix A. Conte, M.D. (by invitation), New York City, N. Y.



NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS (NCRP)

Radiation Protection in Educational Institutions

The publication of recommendations on radiation protection in connection with the use of radiation-producing equipment or materials in educational demonstrations or experiments is announced by the National Council on Radiation Protection and Measurements (NCRP).

NCRP Report No. 32, especially designed for use in teaching institutions, discusses the problem of using devices of our modern technology to teach science at the high school and undergraduate college level. It points up the hazards involved in the use of such devices and describes accepted methods for limiting the exposures to radiation which result from such use. The report emphasizes the responsibility of the science teacher to introduce his students to the phenomena of the "Atomic Age." At the same time, it stresses the need for adequate safeguards against unnecessary exposure resulting from the indiscriminate use of radiation-producing devices or materials.

The report deals with biologic considerations, including somatic and genetic effects; typical radiation sources used in schools; principles of radiation protection; and radiation protection programs. For the first time, the NCRP recommends a dose limit for students exposed as a result of

their educational interest and activity.

The study which resulted in the current report was undertaken at the request of the American Association of Physics Teachers. The Division of Radiological Health, U. S. Public Health Service, assisted in the initial phase of the study by conducting a field survey to define the scope of the problems involved in the use of radiation in teaching institutions.

The publication of NCRP Report No. 32 represents a new development in the NCRP program. This is the first NCRP report published by the Council, a non-profit, Congressionally-chartered corporation, since it came into being as the successor to the National Committee on Radiation Protection and Measurements. Previously, major NCRP reports have been published by the National Bureau of Standards as NBS Handbooks. Copies of the new report, NCRP Report No. 32, *Radiation Protection in Educational Institutions*, can be purchased for \$0.75 each from: NCRP Publications, P. O. Box 4867, Washington, D. C. 20008.

For additional information contact W. R. Ney, Executive Director, National Council on Radiation Protection and Measurements, 4000 Brandywine Street, N. W., Washington, D. C. 20016.



NEWS ITEMS

OAK RIDGE ASSOCIATED UNIVERSITIES

Conference on Principles of Radiation Protection

Recent research in radiation protection and health physics, and opportunities for teaching, research and applied programs in these fields, will be the subject of a special conference conducted by Oak Ridge Associated Universities in Oak Ridge, Tennessee, August 24-26, 1966.

The Conference is sponsored by the U. S. Atomic Energy Commission, and is being presented in cooperation with Oak Ridge National Laboratory.

Participants will be faculty members from larger universities and colleges of liberal arts, as well as from technical institutes and schools of engineering.

Outstanding speakers from AEC installations, universities and research laboratories throughout the nation will conduct the daily lecture sessions. In addition, visits to Oak Ridge installations will enable the participants, lecturers and scientists to discuss problems and programs in the field of radiation protection in greater detail.

Full information about the Conference can be obtained from: Special Projects Office, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, Tennessee 37830.

PUERTO RICO NUCLEAR CENTER

Dr. J. A. del Regato, Director of the Penrose Cancer Hospital of Colorado Springs, has been elected Chairman of the Bio-Medical Advisory Committee of the Puerto Rico Nuclear Center, replacing Dr. Shields Warren of Boston.

The Puerto Rico Nuclear Center is jointly operated by the Atomic Energy Commission and the University of Puerto Rico. Under the directorship of Dr. J. Bugher, the Center has developed a competent staff and a variety of research projects and educational programs involving radiation, in

the fields of medicine, agriculture, terrestrial ecology and marine biology.

Other members of the Bio-Medical Committee, who serve in an advisory capacity are Dr. John D. Cooper, Dean of Sciences Northwestern University; Dr. James Horsfall, Director of the Experimental Agricultural Station of the State of Connecticut and Dr. Paul Pearson, President, Nutrition Foundation, New York City.

NINTH INTERNATIONAL CANCER CONGRESS

The Ninth International Cancer Congress will be held in Tokyo, Japan, October 23-29, 1966.

The opening ceremony will be at the Nippon Budokan on Sunday, October 23. The Harold Dorn Memorial Lecture and the closing ceremony will be held at the Hotel New Otani which is close to the site of the Congress.

The Scientific Program will be centered around Congress Lectures, Panel Discussions and Section Meetings. In addition to a scientific and a commercial exhibition, projection of films will be arranged.

All these activities will be held in five buildings close to one another in the Hirakawa-cho section of the Akasaka area in Tokyo.

The official languages of the Congress will be English and French.

For further information concerning the Congress, please write to: Japanese National Organizing Committee for the Ninth International Cancer Congress, Secretariat c/o Cancer Institute, Nishisugamo 2-chome, Toshima-ku, Tokyo, Japan.

INTERAMERICAN COLLEGE OF RADIOLOGY

Revista Interamericana de Radiología

As stated in the November, 1965, issue of this JOURNAL (p. 788), the Board of Di-

rectors of the Interamerican College of Radiology, at its meeting held on October 7, 1964, at Caracas, Venezuela, elected Dr. Oscar Soto of Lima, Perú, as the new President for the term 1964-1967, and delegated to him the power to nominate an Editor of the official organ of the College and to choose the place where it should be published.

Dr. Soto appointed Dr. Guillermo Pezet M. Q., Lima, Perú, as the Editor and has chosen Lima, Perú, as the place of publication.

The *Revista interamericana de radiología*, as the "Órgano Oficial del Colegio Interamericano de Radiología," is the product of this arrangement. Its Volumen I, No. 1, appeared in January, 1966. In an inspiring Editorial, Dr. Soto specifies that the aims, besides reporting the scientific activities of its members, according to the By-Laws of the College, are "to protect the jurisdiction of Radiology, to stimulate the development and improvement of radiological practice and teaching in our continent, and to foster the creation of Radiology Associations as well as the celebration of Interamerican Congresses of this specialty."

Commensurate with these important aims, Volume I, No. 1, contains an impressive number of articles on teaching of radiology in the Americas. They are written by

Professor Oscar Soto of Lima, Perú; Dr. Leandro Zubiaurre, Montevideo, Uruguay; Dr. Baudelio Villanueva, México, México; Dr. Eugene P. Pendergrass, Philadelphia, U.S.A.; Dr. Philip J. Hodes, Philadelphia, U.S.A.; and Dr. Francisco P. Cifarelli, Rosario, Argentina. The articles of Dr. Walter Bomfim Pontes of Brazil and Dr. Amadeo Riera S. of San Salvador on the same subject will be published in a subsequent issue.

The second part of the Journal contains articles on scientific contributions such as microradiology; chemotherapy and radiotherapy; study of hepatic neoplasms by celiac angiography; indications of bronchography in benign lesions of the lung; contrast media used for angiography; and fibrosarcoma of the bone.

All in all, *Revista interamericana de radiología* represents a notable addition to the world's radiologic periodicals, reflecting the enthusiastic efforts of Dr. Oscar Soto, the President of the Interamerican College of Radiology and Dr. Guillermo Pezet M. Q., the Editor of its official organ.

Original articles offered for publication and other correspondence pertaining to the editorial management should be sent to Instituto de Radiología "Cayetano Heredia," Hospital Arzobispo Loayza, Av. Alfonso Ugarte, Lima, Perú.

It is with deep regret that we announce the death on May 21, 1966 in Tucson, Arizona, of Dr. Ursus V. Portmann, Past President of the American Roentgen Ray Society and distinguished member of the Consulting Editorial Board of this JOURNAL.



BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

TRATTATO DI RADIODIAGNOSTICA. Volume I, in 2 Parts. Edited by Luigi Turano, Direttore dell'Istituto di Radiologia dell'Università di Roma. Cloth. Pp. Tomo primo, 612, and Tomo secondo, 503, with many illustrations. Price, Volume I, Tomo 1 and 2, L. 30,000. Unione Tipografico-Editrice Torinese, Corso Raffaello 28, Torino, Italy, 1965.

Between 1930 and 1940 Italian Radiology was led by a great teacher, Aristide Busi, who occupied the chair of Radiology at the University of Rome and established the first post-graduate training programs in Italy. After Busi's death his classic book "A Manual of Diagnostic Radiology" continued to be used by most of the teachers and trainees. Times, however, change and the many recent developments in diagnostic Radiology clearly indicated the need for a new basic Italian text book in a class with those edited by Schinz, Shanks and Golden. This task has been undertaken by one of Busi's most vigorous pupils, Professor Luigi Turano, who now occupies the chair of Radiology in Rome and who is well known in this Country, having presided over the last International Congress.

Over the years, Professor Turano has trained many young people and has worked with most Italian radiologists. This has enabled him to gain the collaboration of some of the best men in his country. The two Parts of Volume I of this new book have just appeared and are excellent in form, content, illustrations and teaching value. Several other volumes are in the course of preparation and if they are as good as the first, Professor Turano and his collaborators will have given the Italian teachers of Radiology some outstanding tools for the training of the next generation of radiologists.

In the first chapter of Part I, Professor Turano explains the fundamental concepts of the radiological method and discusses the importance of the clinical-radiological approach to the individual patient. This chapter is important because it sets the tone of the whole book.

The following chapter by G. Biagini is concerned with the basic electrical knowledge needed by radiologists and with the physical factors of diagnostic radiology. This chapter is well done and condenses much practical information within 127 pages. The general principles of radiological technique are discussed in the next chapter by G. Giannardi and S. Squillaci, who describe the factors involved in ordinary and high voltage work, in orthography, photo-fluoroscopy, teleroentgenography, plesigraphy, microradiography, stereography, tomography, plastic reconstruction, seriography, cine-techniques, kymography and closed circuit television. The chemistry, physiology and clinical use of radiological contrast media are discussed thoroughly by L. Ciarpaglini.

G. Scarpa describes the radiological diagnosis of laryngeal disease, then L. Turano writes a masterful dissertation (326 pages) of the radiology of the trachea, bronchi and lungs. The coverage given these organs is complete, the text clear and the illustrations excellent. Pleural diseases are well described by L. Pigorini.

Part II begins with the radiology of the mediastinum, great vessels and heart. This section (350 pages) is written with competence and skill by G. De Giuli and P. Gambaccini, who discuss in an integrated fashion the data furnished by the history, clinical examination, cardiac catheterization, fluoroscopy, electrocardiography, kymography, and cardioangiography in the many conditions affecting the mediastinum, great vessels and heart. Peripheral angiography and splenoportography are described by Giannardi and De Dominicis while lymphography is a subject well developed by Bompiani, Fanucci and Loasses.

The tenor of Volume I is one of interrelation of the basic clinical, laboratory and radiological data. The specialist within the specialty may wish for greater detail on some subjects, but for general diagnostic purposes the authors have succeeded splendidly and their performance promises that the following volumes will match the excellence of the first.

The Publishing House, U. T. E. T. of Turin, has done outstanding work in presenting the material in a faultless form.

CESARE GIANTURCO, M.D.

ATLAS OF RADIATION DOSE DISTRIBUTIONS.

Volume I. Single-Field Isodose Charts. Compiled by E. W. Webster, Department of Radiology, Massachusetts General Hospital, Boston; and K. C. Tsien, of the International Atomic Energy Agency. Cloth. Pp. 55, with 155 charts. Price, \$15.00. International Atomic Energy Agency, Vienna, 1965. Distributed by International Publications, Inc., 317 East 34th Street, New York, N. Y. 10016, 1965.

As stated in the Foreword, the International Atomic Energy Agency (IAEA) has undertaken since its establishment, as an important part of its program, the collection and dissemination of information on radioisotopes and radiation sources to assist Member States in acquiring knowledge and skills in their application.

In the field of radiation therapy, the Agency in the last 5 years has given its attention to dosimetry and provision of physical data on dose distributions, in the form of isodose charts relating to media irradiated with roentgen-ray and gamma-ray beams under different conditions. For the 250 Kv. single field roentgen irradiation, the isodose charts sponsored by the Agency have already been published by Butterworth, London, England.

Since early 1960, the Agency made surveys of the available isodose charts of Co^{60} , Cs^{137} , high energy roentgen-ray and electron beam accelerator therapy.

The present Volume I is one of three making up an *Atlas of Radiation Dose Distributions*. It was compiled by E. W. Webster of the Department of Radiology of the Massachusetts General Hospital, Boston, and by K. C. Tsien, formerly of the Department of Radiotherapy, Temple University Medical Center, Philadelphia, and presently of the IAEA. It contains a selection of single-field isodose charts of Co^{60} , and Cs^{137} gamma-rays, and of a wide range of high energy roentgen-rays (2-70 MV) and electron beams (7-35 MeV). Some charts illustrate the effects on the isodose patterns of wedge filters and of absorbers which modify field shape. Also, particular attention is given to variations in depth dose and in curvature of

isodose lines produced by the wide range of physical factors.

Volume II and III, which will be published in the near future, will present isodose charts and graphs for multiple fields and moving fields, respectively, together with analytic studies.

The charts of Volume I were selected from 48 institutions and 11 different countries. They are presented full size and bound in a handsome volume, designed for easy perusal and reference. Indices are included to facilitate selection of type of apparatus or type of physical factors to be investigated.

The *Atlas of Radiation Dose Distributions* is an extremely valuable asset for comparative radiotherapeutic planning, by taking into consideration the importance of the many physical variables involved.

T. LEUCUTIA, M.D.

BOOKS RECEIVED

GASTROSCOPIC PHOTOGRAPHY. By Robert S. Nelson, M.D., Internist and Chief, Gastroenterology Section, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Pp. 122, with 48 illustrations. Price, \$9.75. Year Book Medical Publishers, Inc., 35 E. Wacker Drive, Chicago, 1966.

A SEARCH FOR GENETIC EFFECTS OF HIGH NATURAL RADIOACTIVITY IN SOUTH INDIA. By H. Gröneberg, G. S. Bains, R. J. Berry, Linda Riles, C. A. B. Smith and R. A. Weiss. Medical Research Council: Special Report Series No. 307. Paper. Pp. 59, with many illustrations. Price, 11s. Od. net. Her Majesty's Stationery Office, Atlantic House, Holborn Viaduct, London, England, 1966.

I RADIOISOTOPI PER APPLICAZIONI INTERNE IN DIAGNOSTICA E TERAPIA. By A. Laconi, with the collaboration of F. Caffarelli, L.D., and F. Melfi, L.D. Cloth. Pp. 661, with some illustrations. Price, 18,000 L. Sansoni-Firenze, Palermo, 1966.

BASES HEMODINAMICAS CLINICA CARDIOVASCULAR. By Juan J. Puigbo, Pablo Blanco, Ivan Machado, and Hugo Giordano de la Sección de Hemodinamia del Servicio de Cardiología del Hospital Universitario. Cloth. Pp. 472, with 247 illustrations. Universidad Central de Venezuela. Organización de Bienestar Estudiantil, Servicio de librería, Plaza del Rectorado, Caracas, Venezuela, 1966.

HUMAN PALAEOPATHOLOGY. Proceedings of a Symposium on Human Palaeopathology, held in Washington, D. C. January 14, 1965, under the auspices of the Subcommittee on Geographic Pathology, National Academy of Sciences-National Research Council. Edited by Saul Jarcho. Cloth. Pp. 182, with some illustrations. Price,

- \$7.50. Yale University Press, 149 York Street, New Haven, Conn., 1966.
- DIAGNOSTIK DER KNOCHEN- UND GELENKKRANKHEITEN NACH FÜHRENDEN RÖNTGENSYMPTOMEN. By Prof. Dr. P. Deák, Leiter des Lehrstuhls für Röntgenologie, Institut für Ärztliche Fortbildung Budapest. Cloth. Pp. 546, with 354 illustrations. Price, \$17.00. Akadémiai Kiadó, Publishing House, Budapest V. Alkotmány U. 21, 1966.
- EPIDEMIOLOGICAL APPROACHES TO THE STUDY OF CANCER AND OTHER CHRONIC DISEASES. National Cancer Institute Monograph 19, January, 1966. Edited by William Haenszel. Cloth. Pp. 465, with many tables. Price, \$3.75. U. S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, Bethesda, Md. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., 1966.
- SELECTED PAPERS FROM THE INSTITUTE OF CANCER RESEARCH: ROYAL CANCER HOSPITAL AND THE ROYAL MARSDEN HOSPITAL, 1964. Volume 19. Published by the order of the Committee of Management of the Institute and the Board of Governors of the Royal Marsden Hospital, London. Cloth. Pp. 1172, with many illustrations. The Chester Beatty Research Institute, Fulham Road, London, S. W.3, England, 1966.
- ANNUAL REVIEW OF MEDICINE. Arthur C. de Graff, Editor, New York University College of Medicine; William P. Creger, Associate Editor, Stanford University School of Medicine. Volume 17. Cloth. Pp. 564. Price, \$8.50. Annual Reviews, Inc., 231 Grant Avenue, Palo Alto, Calif., 1966.
- THE RADIOLOGIC CLINICS OF NORTH AMERICA. April, 1966, Volume IV. Symposium on Neuroradiology. Guest Editors, Maxwell H. Poppel, M.D., and Harold G. Jacobson, M.D. Cloth. Pp. 238, with many illustrations. W. B. Saunders Company, West Washington Square, Philadelphia, 1966.



ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

ABDOMEN

WYATT, GEORGE M., THORNBURY, JOHN R., FISCHER, HARRY W., and HIERSCHBIEL, ERNST A. Comparison of ammonium alum and tannic acid as barium enema additives. *J.A.M.A.*, Feb. 14, 1966, 195, 537-540. (Address: Dr. Wyatt, 214 N. Van Buren Street, Iowa City, Iowa.)

The authors report on their use of ammonium alum in lieu of tannic acid after the FDA issued a statement disapproving the use of tannic acid in enemas.

Investigative work was begun on animals, the results of which indicated that comparable postevacuation colon contraction and coating could be obtained with alum; however, the degree of contraction and coating was never equal to that seen in human subjects using 0.75 per cent tannic acid. No gross or microscopic evidence of intestinal or systemic injury due to alum was seen in any of the animals who were sacrificed. Eight rabbits given 10 per cent alum solution intravenously (6 to 100 mg./kg.) showed no clinical or histologic evidence of toxicity 2 to 6 days later.

After administration of a barium enema containing 1 per cent ammonium alum to one of the investigators showed good roentgen definition without complications, two separate studies on patients were done to compare tannic acid and alum as additives to barium enemas. The investigations were done under double-blind protocol and data evaluated by computer. A control group was given barium only.

The alum concentration was 1 per cent and the tannic acid preparation used was 0.75 per cent. Timing of the postevacuation roentgenograms was started upon completion of fluoroscopy.

The results indicate that alum is as effective as tannic acid in producing colon contraction but does not maintain the mucosal pattern as well if the postevacuation roentgenograms are taken at intervals longer than 25 minutes. Side effects—cramping, nausea, weakness—were equal in both groups but did not occur in the control group. The studies show that the use of either additive increased the incidence of effective colon contraction and mucosal coating.—*Lois Cowan Collins, M.D.*

ELLMAN, B., McLEOD, I. N., and POWELL, S.J. Diagnostic pneumoperitoneum in amoebic liver abscess. *Brit. M. J.*, Dec. 11, 1965, 2, 1406-1407. (Address: Dr. S. J. Powell, Amoebiasis Research Unit, P. O. Box 1035, Durban, South Africa.)

The authors recommend the use of intraperitoneal gas as a supplemental aid where difficulty is experienced in establishing the diagnosis of subphrenic

disease. Hepatic amoebic abscesses are predominantly in the right lobe of the liver and can extend upward to the right hemidiaphragm with resultant adhesions.

Proof in most diagnoses is first by aspiration of typical pus or by pus coughed up by way of hepato-bronchial fistula, with most of the remaining cases diagnosed by clinical findings and antiamebic therapy response. A small remaining group exhibits only obscure findings difficult to differentiate as to lung or liver origin. These are the cases best subjected to pneumoperitoneum.

Thirty diagnostic problem cases were selected, of which 17 had hepatodiaphragmatic adhesions. All but one of these responded well to antiamebic therapy and 8 had typical pus aspirated near these adhesions.

Eight cases showed generalized or localized elevation of the diaphragm with 5 exhibiting localized convex superior margin liver deformity. In 5, tomography demonstrated abscesses within the liver, yielding diagnostic pus.

One patient not responding to medication had a subtotal gastrectomy for perforated gastric ulcer 4 months previously and a diagnosis of pyogenic subdiaphragmatic abscess was made.—*Sam Campbell, M.D.*

GYNECOLOGY AND OBSTETRICS

BORTOLOTTI, G., and SANTORO, P. Studio comparativo dei quadri pneumopelvigrafici e dei reperti chirurgici nelle affezioni utero-annexiali. (Comparative study of the pelvic pneumographic changes and the surgical findings in uterine-annexial diseases.) *Riv. radiol.*, 1965, 5, 701-716. (From: Reparto di Radiologia, Pio Istituto di Santo Spirito ed Ospedali Riuniti di Roma and Ospedale S. Eugenio, Rome, Italy.)

A group of 14 female patients with lesions in the pelvis was studied by pelvic pneumography and the roentgenologic findings were compared with the anatomic-pathologic changes observed later at surgery.

The cases included: 1 myoma of the uterus, 2 dermoid cysts of the ovaries, 4 ovarian cysts, 6 retention cysts of the ovary, and 1 case of retention cyst of the ovary in a patient at the 8th week of pregnancy.

In 13 cases the uterus and the adnexa were satisfactorily demonstrated. In the case with myoma of the uterus an incomplete pelvic pneumography was obtained because of diffuse adhesions, confirmed later at surgery.

In all cases the roentgenologic conclusions as to the size, shape and position of the pelvic masses were confirmed at surgery.—*A. F. Govoni, M.D.*

GENITOURINARY SYSTEM

FIUMICELLI A., CASTRUCCI, A., and DEL DUCA, Th. Tomografia multipla simultanea del rene

in corso di angiografia renale selettiva. (Simultaneous multiple tomography of the kidneys during selective renal angiography.) *Radiol. med.*, Nov., 1965, 51, 1200-1204. (Address: Dott. Prof. Aligi Fiumicelli, Via Fra'Bevignate, 14, Perugia, Italy.)

Selective renal angiography is a very important roentgenologic procedure in the evaluation of pathologic changes involving the kidneys. There are times, however, when the roentgen findings are not confirmed at surgery.

Lately, the authors have been studying the so-called "vascular lacunae," which appear in the nephrographic stage as areas of radiolucency in the otherwise radiopaque parenchyma.

In order to better evaluate these findings, selective renal angiography is performed on a multi-directional tomographic table. If it is thought that the angiographic study is not satisfactory because of a poor nephrographic stage, 6 to 7 cc. contrast medium is injected once more and 7 seconds after the end of the injection, tomographic studies are made with a multi-section cassette at pre-selected layers.

It is felt that this technique of simultaneous multiple nephrotomography is of great value in the evaluation of vascular lacunae noted at times in selective renal angio-nephrograms.—*A. F. Goonni, M.D.*

SHORT, D. W., KENNEDY, A. C., LUKE, R. G., and MACKEY, W. A. Renovascular hypertension in aortic arch syndrome due to Takayasu's arteritis. *Brit. J. Surg.*, Dec., 1965, 52, 963-965. (From: University Departments of Surgery and Medicine, Glasgow Royal Infirmary, Glasgow, Scotland.)

If hypertension develops in a patient with primary arteritis, isotope renography and intravenous pyelography are simple and dependable procedures useful in the detection of renal ischemia. The authors report on a patient with nonprogressive aortic arch syndrome who was observed for 6 years before she presented with symptoms suggestive of renovascular hypertension. Intravenous pyelography showed increased density and spasticity of calyces on the left; isotope renography indicated delayed transit time through the left kidney. Split function studies showed reduced volume and sodium content from the left kidney and increased concentration of creatinine and urea. Electrocardiography revealed left ventricular strain. Aortography showed stenosis of the left common carotid artery, irregularity of the wall of the lumbar aorta, a single stenosed left renal artery, and a double but normal right renal artery.

At operation the left renal artery was dissected from surrounding dense peri-arterial fibrosis after which simultaneous direct aortic and renal artery pressures showed no gradient. Therefore, no further attack upon the renal artery was attempted. In a 2

year follow-up, the patient's improvement has been very satisfactory: renal function has improved and hypertension has decreased in severity.

The authors believe that this is the first reported case of correction of renovascular hypertension in primary arteritis through conservative surgical technique. The dominant feature in this case appeared to be peri-arterial fibrosis which had embedded the abdominal aorta and proximal portion of the left renal artery in a dense and constricting fibrous sheath. In other reported cases the authors have felt that the primary lesion was a peri-arteritis involving the adventitia and that the process sometimes progressed to involve all layers of the vessel wall.—*Lois Cowan Collins, M.D.*

LALLI, ANTHONY F. The roentgen diagnosis of renal vein invasion by tumor. *J. Urol.*, Jan., 1966, 95, 8-9. (From: Department of Radiology, University of Michigan Medical Center, Ann Arbor, Mich.)

Five patients with renal cell carcinoma demonstrated nonvisualization on excretory urography and typical changes of a renal mass on retrograde pyelography.

The author considers the sign of nonvisualization as indicative of renal vein invasion. In 1 of the 5 patients, the renal vein was compressed and invaded, but there was no intraluminal tumor seen at the time of the pathologic study. This patient had a somewhat better prognosis than those who had actual tumor within the lumen of the renal vein. The preoperative demonstration of this sign indicates a poor prognosis and is therefore useful in the determination of the treatment of the patient.

One table is presented summarizing the clinical and pathologic findings in all 5 cases and a composite figure shows the roentgen findings in a typical case.—*George W. Chamberlin, M.D.*

AL-GHORAB, M. M., EL-BADAWI, A. A., and EFFAT, H. Vesico-ureteric reflux in urinary bilharziasis: a clinico-radiological study. *Clin. Radiol.*, Jan., 1966, 17, 41-47. (From: Department of Urology and Department of Radiology, Faculty of Medicine, University of Alexandria, Alexandria, U.A.R.)

The main brunt of infection in urinary bilharziasis falls on the bladder and the lower ends of both ureters. Among the commonest radiologic manifestations encountered in bilharzial patients is a dilated pelvic segment of the ureter.

The authors investigated 70 consecutive patients with urinary bilharziasis. The aim of this article is to point out the role of vesico-ureteric reflux in producing dilatation of the ureter in this disease, and its bearing upon the function and radiologic appearances of the renal tract. In this group of 70 pa-

tients vesico-ureteric reflux was demonstrated in 31. This was unilateral in 17 and bilateral in 14 cases. In 36 refluxing ureters the contrast material ascended to the kidney and filled the pelvi-calyceal system. In the remaining 9 ureters it stopped at or a little below the pelvic brim.

The authors could not define a clinical syndrome that is characteristic or even suggestive of reflux. Renal pain that develops or increases during the act of micturition is rarely noted in the absence of reflux. A cystoscopic sign that may help in the diagnosis is a patulous ureteric orifice. Vesico-ureteric reflux may occur in a urinary tract which appears normal in the intravenous urogram. Ascending urography is the only means available for diagnosing ureteric reflux, and every bilharzial patient who has a dilated unobstructed ureter must be so investigated.

Based upon the known pathology of urinary bilharziasis, some anatomic features may be blamed for the occurrence of reflux. The most important are fibrosis of the intramural part of the ureter with consequent rigidity and shortening, degeneration and/or fibrosis of the trigonal muscle, and gaping of the ureteric orifice by surrounding bladder fibrosis. Infection is also an important factor.

Several surgical techniques have been proposed to correct reflux. None of these seem to be applicable to the bilharzial cases in which the extensive fibrosis and often gross dilatation of the ureter, the fibrosis of the bladder with frequent shortening of the trigone and the diffuse affection of the mucosa would preclude a satisfactory result. A new surgical approach is needed to suit the bilharzial cases.—*Samuel G. Henderson, M.D.*

GOLDSTEIN, ARTHUR G., and CONGER, KYRIL B. Perforation of the ureter during retrograde pyelography. *J. Urol.*, Dec., 1965, 94, 658-664. (From: Department of Urology, Temple University Medical Center, Philadelphia, Pa.)

The authors report on 13 cases of ureteral perforation with extravasation of contrast medium during the performance of 8,000 retrograde pyelographies, an incidence of 0.16 per cent.

The diseased ureter is more prone to perforation than the normal ureter. Perforation of the diseased ureter most often occurs distal to a calculus or stricture. Perforation of a normal ureter is observed most commonly at the ureterovesical junction and less commonly at the ureteropelvic junction. Other factors which contribute to ureteral perforation are the use of stylets, repeated examinations with a brief interval between instrumentation, forceful and careless instrumentation or the exertion of too much pressure during injection of the contrast material. This last factor occurred in 4 patients with the use of the Braasch bulb. Since this bulb is used in patients with

an obstructed ureter and when ordinary catheterization has been unsuccessful, the application of the bulb and the injection of the contrast material through the catheter should be done with great care.

Ureteral perforation can be recognized immediately by the localization of pain at the site of the injection. Difficulty in passing the catheter or absence of urine flow through the catheter should make the operator suspicious of an extraluminal placement. The diagnosis is confirmed by noting extravasation on the pyelogram. Clinically, fever, chills, nausea, vomiting, and abdominal pain may occur and last for several days. The majority of the cases clear up with conservative treatment, and in the authors' series no patients required surgical drainage. Excretory urography, a few days after perforation, is indicated to eliminate the possibility of obstruction or other damage to the ureter. All patients with perforated ureters should be hospitalized until the danger of extravasation and abscess formation has passed.

The authors include 12 single and composite roentgenographic reproductions to illustrate the various types of ureteral extravasation.—*George W. Chamberlin, M.D.*

BRODEUR, ARMAND E., GOYER, ROBERT A., and MELICK, WILLIAM. A potential hazard of barium cystography. *Radiology*, Dec., 1965, 85, 1080-1084. (From: Departments of Radiology, Pathology, and Urology, Cardinal Glennon Memorial Hospital for Children, and St. Louis University School of Medicine, St. Louis, Mo.)

The authors report an unusual complication of cystourethrography in children with the utilization of micropaque barium. Micropaque was employed in preference to urokon or dionosil as previous reports had indicated no complications from its use, whereas the other agents have been found to be irritating to the urethra, resulting in refusal to void, especially in small children.

A sterile suspension of 150 ml. of micropaque in a liter of physiologic saline was used in this study. This suspension was injected into the bladder of 100 children with urinary tract symptoms and roentgenograms were taken during injection and micturition. In the first 99 patients, excellent results were obtained without evidence of urethral irritation or other complications. Of these children, 17 showed ureteral reflux and 4 also showed renal reflux. However, in the 100th child, renal reflux resulted in sudden opacification of the renal parenchyma. For about 2 months following this, renal tubular casts containing barium particles were found in the urine and roentgenograms taken periodically showed the renal parenchymal barium still present after 6 months.

Following this complication, the studies with micropaque were discontinued and experimental studies were undertaken to determine the effect of

micropaque on a pig's kidney. The pig's ureter was exposed and ligated and micropaque injected above the ligature. Fluoroscopy revealed almost immediate extravasation into the outer cortex and beneath the renal capsule. Biopsy specimens taken at selected intervals showed initial occlusion of the tubules with barium with rupture of the pericapsular tubules and extravasation of barium into the parenchyma and beneath the capsule. This progressed to clearing of most of the tubules but with an acute inflammatory reaction in the peripheral parenchyma and finally (in 2 weeks) to a chronic inflammatory parenchymal picture with extensive interstitial fibrosis and atrophy of many of the tubules, probably from persistent distal tubular obstruction. The subcapsular barium remained in its original location.

From these studies the authors conclude that barium enters the nephrons by retrograde flow from collecting tubules communicating with the renal pelvis and that small amounts of ascending pressure easily rupture that portion of the nephron at the periphery of the cortex with resultant parenchymal and subcapsular extravasation. Most of the nephrons are soon cleared of barium but the granulomatous reaction from the parenchymal barium is severe and may result in extensive renal damage. Some tubules also are damaged by retention of barium. The relationship of these findings to possible changes from other diagnostic renal procedures and to obstructive urographies is not known.—*Victor B. Brasseur, M.D.*

ROSSI, PLINIO, KAUFMAN, LEONARD, RUZICKA, FRANCIS F., JR., and PANKE, WILLIAM. Angiographic localization of pheochromocytoma. *Radiology*, Feb., 1966, 86, 266-275. (From: Department of Radiology, St. Vincent's Hospital and Medical Center, New York, N. Y.)

In the past, hypertensive patients in whom pheochromocytoma was suspected were examined by conventional roentgenographic techniques only. Recently, however, clear demonstrations of this tumor have been obtained following the injection of contrast medium into the aorta, or after selective renal artery catheterization.

Usually three arteries supply the suprarenal gland, but the great variation in number and origin of the suprarenal arteries and their small caliber and the superimposition of other arteries in aortography make their identification difficult. However, the inferior suprarenal artery, by virtue of its origin from the renal artery, can be clearly visualized by selective renal catheterization. The authors believe this, in addition to the preliminary aortogram, to be a *sine qua non* in the definitive demonstration of pheochromocytoma.

Six cases, one of which was malignant, are reported. All were later surgically proved. Using the Seldinger percutaneous technique, all were demon-

strated and localized by means of aortography. The finely reticulated arterial pattern, absence of arteriovenous shunts, and a well-defined and homogeneous tumor stain in the capillary phase are described as the characteristic angiographic findings of benign pheochromocytoma. Malignant pheochromocytoma is characterized by irregular newly formed vessels, early venous drainage, and a poorly defined capillary phase. No complications were encountered during or after the angiographic studies.—*Howard R. Stewart, M.D.*

SCHNUR, BERNARD M., and SAKSON, JOHN A. Trans-sacral retroperitoneal pneumography. *J. Urol.*, Dec., 1965, 94, 701-705. (From: Department of Radiology, St. Francis Hospital, Trenton, N. J.)

The authors describe a new approach to the retroperitoneal space through the penultimate sacral foramen. This is based upon the fact that the ultimate and the penultimate sacral foramina are normally 20 mm. from the midline in the adult patient. The presacral space at the level of the penultimate sacral foramen is normally occupied with spider-web alveolar tissue so that the rectum recedes freely with minimal pressure. This space may be as small as 6 mm. when the rectum is distended but with displacement of the posterior rectal wall, it can be expanded to 4.5 cm.

The technique is to prepare the patient with 2 ounces of castor oil. He is placed prone on the roentgenographic table and a routine roentgenogram is made for position and technical factors. Two parasagittal ink lines are inscribed on the patient's skin overlying the lower sacral segment, exactly 20 mm. from the midline. The skin surface is then cleansed and draped. A small amount of 1 per cent procaine is injected over the penultimate foramen which is approximately 2-3 cm. from the sacrococcygeal junction and along the ink lines previously drawn on the skin. After the needle is placed in the foramen, a 50 cc. syringe is attached and 20-25 cc. of air is injected with minimal thumb pressure. This will displace the posterior rectal wall. The carbon dioxide tank is then attached and 1,500-2,000 cc. of carbon dioxide is insufflated through a flow valve in 1 minute unless there is evidence of obstruction such as might be produced by previous disease in the retroperitoneal space.

The patient is instructed to verbalize on the location of his sensation of distention. In patients who have previous partial obliteration of the retroperitoneal space, early anterior suprapubic discomfort is noted. In the normal retrorectal space, however, upper anterior abdominal discomfort has been invariably accurate in predicting subsequent visualization of gas in the perirenal and retroperitoneal space.

Following injection of 2,000 cc. of CO₂, appropriate roentgenograms are made in the posteroanterior

and oblique projections. If further information is necessary, an additional 2,000 cc. may be administered and the distribution of the gas may be controlled by elevating the side under observation or by placing the patient in the erect position. CO₂ is usually absorbed in 15–20 minutes.

The advantages of this method are the accuracy of placement of the needle in the presacral space, the technical ease of injection of CO₂ with relatively little patient discomfort, and the practically complete elimination of the danger of sepsis. In this technique, there is less likelihood of displacement of the inserted needle in the event that other examinations such as intravenous urography, aortography, or vena cavography are done as concomitant procedures.

The authors have used this technique in 42 instances without complication. They report that the method is easy, relatively rapid, and reliable.

Five composite figures show the anatomy of the sacrum and the presacral space.—*George W. Chamberlin, M.D.*

NERVOUS SYSTEM

STEWART, BRUCE H., DIMOND, ROBERT L., FERGUSON, CLIFTON F., and SHEPARD, PHILLIP B. Experimental renal arteriography: comparison of spinal cord and renal toxicity from iothalamate and diatrizoate compounds. *J. Urol.*, Dec., 1965, 94, 695–700. (From: Department of Surgery, Section of Urology, University of Michigan Medical Center, Ann Arbor, Mich.)

This is an evaluation in dogs of a number of different contrast media commonly used for aortography and their toxic effects on the kidneys and spinal cord.

A total of 255 dogs was anesthetized and the contrast material was injected through a catheter, the tip of which was placed at about the level of the renal vessels. After a specimen of blood was removed for urea nitrogen and serum creatinine tests, a preselected dose of contrast medium was manually injected at a rate of 3 cc. per second. Roentgenograms were taken during the early series; but when renal arteriograms of good quality were consistently obtained, filming was discontinued in order to save time and expense. The occurrence of any immediate neurologic reaction was recorded, the catheter was then removed, and the incision closed. On the first postoperative day, determinations were made of blood urea nitrogen and serum creatinine levels, and the dogs were carefully examined for neuro-muscular disorders, such as weakness, ataxia, or paralysis. The dogs were sacrificed after 7 days of observation.

There were no significant changes between the pre-injection and post-injection blood urea nitrogen or serum creatinine levels in any of the dogs studied. It was concluded that the intra-aortic injection of

iothalamate or diatrizoate compounds in doses up to 3 cc. per kilogram of body weight will not result in appreciable renal damage and thus these agents are quite safe from this standpoint.

There was considerable difference in the spinal cord toxicity depending upon the agent and the dose used. In a series of 103 animals, single injections of either angio-conray or hypaque M-90 per cent were made in doses of 3 cc., 1 cc., or $\frac{1}{2}$ cc. per kilogram of body weight. Angio-conray was shown to be toxic in doses of 3 cc. and 1 cc. per kilogram, whereas hypaque showed fewer and less severe spinal cord side effects. The methylglucamine salt of angio-conray was specially prepared to a viscosity similar to that of hypaque 90. This preparation did not produce the severe neuro-toxic reactions produced by the sodium salt of angio-conray.

Preparations of medium iodine content were tested against each other and of these a new compound, the N-methylglucamine salt of iothalamate produced the least number of toxic reactions on the spinal cord.

Special solutions with varying pH values showed that the preparations with pH ranging from 7.1 to 7.3 gave the optimum results in the reducing of the number of side reactions on the spinal cord.

Multiple injections were evaluated by repeating injections a few minutes apart but with a total dose similar to the single total dose. There is very slight increased risk to the spinal cord by repeated injections provided the total dose is not excessive.

The authors conclude that angio-conray carries a significantly high risk of spinal cord damage when used for renal and aortic arteriography. Conray-400, hypaque M-75 per cent and renografin 76 per cent combine satisfactory radiodensity with a relative lack of neuro-toxicity. A new compound, the N-methylglucamine salt of an intermediate concentration iothalamate combines satisfactory radiographic properties with an extremely high range of safety and deserves further study as a contrast agent. The viscosity and the pH of the agent have an important role in the over-all neuro-toxicity of the drug.—*George W. Chamberlin, M.D.*

ROSENCRANTZ, MAGNUS. A case of fibrous dysplasia (Jaffe-Lichtenstein) with vertebral fracture and compression of the spinal cord. *Acta orthop. scandinav.*, 1965, 36, 435–440. (From: Roentgen Department II, and Orthopaedic Department, University of Gothenburg, Sweden.)

Polyostotic fibrous dysplasia occurs most commonly in the femur, tibia, pelvis, or humerus. Involvement of the vertebral column has been reported as infrequent or rare—29 out of about 300 cases.

The author summarizes a very interesting case in which an 18 year old boy was found to have fibrous dysplasia of the thoracic vertebrae presenting with paraplegia. Changes were also found in the skull,

ribs, right scapula, and both hands. Roentgenographic examination revealed severe wedging of D-6 with only a fragment of the vertebral body remaining in the right angled gibbus deformity which was produced.

In spite of unchanging roentgenographic signs, the symptoms of spinal cord compression entirely disappeared on conservative treatment consisting of bedrest and plaster cast. To prevent recurrence, a posterior spinal fusion was done.

One year later the patient remained asymptomatic even though the angulation of the gibbus increased.

Fibrous dysplastic lesions are not roentgenographically characteristic, except in the skull. These multiple cyst-like expansive lesions, sparing the epiphyses and mainly unilateral, may increase in severity and even new lesions may appear until the epiphyses close.

Early diagnosis and treatment of these lesions is very important. Complications such as fracture or pressure symptoms may arise if untreated. In the reported case conservative treatment appears to have been sufficient.—*W. J. Carmony, Jr., M.D.*

HEINZ, E. RALPH, SCHLESINGER, EDWARD B., and POTTS, D. GORDON. Radiologic signs of hydromyelia. *Radiology*, Feb., 1966, 86, 311-318. (From: Departments of Radiology and Neurological Surgery, Columbia-Presbyterian Medical Center, New York, N. Y.)

Immediately after the neural tube of the normal embryo closes it becomes distended, because fluid forms within it more rapidly than it can escape. Since this distention affects the central canal of the cord as well as the cerebral ventricles, it follows that both hydrocephalus and hydromyelia are physiologic in embryonal life. If this fluid filters through the semipermeable rhombic roof in sufficient quantity to dissect open the developing subarachnoid spaces, the central canal of the spinal cord closes. Hydromyelia results if the central canal does not close but remains pathologically dilated.

The authors present 4 cases with observations which give a better understanding of this entity. All 4 cases show the "collapsing cord sign" of hydromyelia. This sign is important in the differential diagnosis of a solid *versus* a cystic lesion of the cord. Patients should be studied with pantopaque myelography, followed by air myelography. An effort should be made to introduce pantopaque within the fourth ventricle. Air myelograms should then be obtained in the semierect or erect position to see if the enlarged cord collapses. Collapse indicates a cystic cause rather than an intramedullary neoplasm.—*A. W. Sommer, M.D.*

SKELETAL SYSTEM

BEBER, BERNARD A., LITT, RICHARD E., and ALTMAN, DONALD H. A new radiographic finding in mongolism. *Radiology*, Feb., 1966, 86, 332-333. (From: Departments of Pediatrics and Radiology, Variety Children's Hospital, University of Miami School of Medicine, and Variety Children's Research Foundation, Miami, Fla.)

A heretofore unreported roentgenographic sign in mongolism is described.

Because of the finding of only 11 pairs of ribs in an infant who was clinically mongoloid, the authors reviewed the roentgenograms of 50 children afflicted with Down's syndrome. The presence of 11 pairs of ribs was found in a relatively high percentage of mongoloid children. Thirty-eight per cent of the females and 14 per cent of the males studied had 11 pairs of ribs.—*A. W. Sommer, M.D.*

FRATKIN, MELVIN J., and SHARPE, ALTON R., JR. Familial hypophosphatemia: report of two cases. *J. Clin. Endocrinol. & Metabol.*, Feb., 1966, 26, 174-180. (From: Departments of Medicine and Radiology, Medical College of Virginia, Richmond, Va.)

A rare occurrence of familial hypophosphatemia with rachitic changes in Negro siblings was observed. Criteria used to differentiate this entity from other refractory rickets are: (1) hypophosphatemia associated with a decreased renal tubular reabsorption of inorganic phosphate; (2) rickets or osteomalacia which does not respond to the usual vitamin D therapy; (3) familial occurrence; and (4) absence of related renal abnormalities.

Initially, there is hypocalcemia which causes hyperplasia and hypersecretion of the parathyroid glands; the resultant hyperparathyroidism produces a phosphate diuresis and resorption of bone causing rachitic bone changes. The pathogenesis is believed to be that of decreased calcium absorption from the intestines.

The patients, a 15½ month old Negro boy, and his younger sister, 20 months old when first seen, both had clinical and roentgenographic evidence of rickets. They failed to respond to the usual vitamin D therapy, but both showed improvement after massive doses (100,000 IU for the boy and 25,000 IU per day for the girl). The children had decreased serum calcium and phosphate levels which increased after the massive vitamin D therapy. Follow-up over a number of years shows that both patients are doing well.

The family history is compatible with autosomal or sex-linked dominant mode of inheritance with incomplete penetrance for clinical rickets. History of

possible rickets in both sides of the family raises the question of a recessive mode of inheritance for hypophosphatemia with clinical rickets, which may be the reason for the reported rarity of hypophosphatemic vitamin D refractory rickets in Negroes.—*Lois Cowan Collins, M.D.*

STAPLES, O. SHERWIN. Dislocation of the brachial artery: a complication of supracondylar fracture of the humerus in childhood. *J. Bone & Joint Surgery*, Dec., 1965, 47-A, 1525-1532. (From: Hitchcock Clinic, Hanover, N. H.)

The author reports 4 cases of the rare vascular complication of supracondylar fracture of the humerus in children in which the brachial artery and vein and median nerve were found at operation to have slipped behind the anteriorly displaced distal end of the proximal humeral fragment, so that the neurovascular bundle ran through the fracture line to reach the anterior aspect of the elbow, where it again assumed its normal course.

The difficulties encountered with the brachial artery dislocated in this position are illustrated by the case of a 4 year old child with a markedly deformed elbow in full extension following injury. Roentgenograms demonstrated severely displaced supracondylar fracture of the humerus. Attempts at closed reduction under general anesthesia always resulted in ischemic changes of the arm with loss of radial pulse. Open reduction revealed the previously described condition. Surgical reduction of neurovascular bundle and the fracture resulted in return to normal function subsequently. Two other cases were similar; a fourth case was similar but involved a compound fracture.

Thus, the 4 cases had low, widely displaced supracondylar fractures, oblique fracture lines, and a rotational deformity, but on comparison with 15 other cases with displaced supracondylar fractures, no distinctive diagnostic features appeared, although those with the dislocated neurovascular bundle generally had more severe displacement. The author's assumption is that wide displacement and rotatory deformity allow the neurovascular bundle to slide behind the proximal humeral fragment, but roentgenograms disclose no clue to support this concept or the correct diagnosis prior to attempted closed reduction.

The clinical findings suggestive of dislocation of the brachial artery are: (1) initially normal circulation and sensation in the hand; (2) immediate loss of circulation in the hand and of the radial pulse with flexion, traction, or attempted manipulation; and (3) restoration of circulation with arm in 0 to 30 degrees of elbow flexion.

The author feels that in addition to the standard indications for open reduction of supracondylar

fracture of the humerus, the previously described type intermittent arterial insufficiency should be similarly treated to prevent possibility of Volkman's contracture, or ischemic myositis and neuritis.—*John Truksa, M.D.*

TAKAHASHI, MUTSUMASA, MARTEL, WILLIAM, and OBERMAN, HAROLD A. The variable roentgenographic appearance of idiopathic histiocytosis. *Clin. Radiol.*, Jan., 1966, 17, 48-53. (From: Departments of Radiology and Pathology, University of Michigan, Ann Arbor, Mich.)

Idiopathic histiocytosis, or histiocytosis X, refers to 3 related conditions: eosinophilic granuloma of bone, Hand-Schüller Christian disease, and Letterer-Siwe disease, considered to be different pathologic expressions of the same disorder. The basic process is a histiocytic proliferation of unknown etiology. Solitary eosinophilic granuloma of lung later came to be included in this group.

The clinical, pathologic and radiologic manifestations of 36 histologically verified cases are reviewed. In all cases the lesions were characterized histologically by a diffuse proliferation of histiocytes. Superimposed upon this basic alteration were variable numbers of eosinophilic leukocytes.

Eosinophilic granuloma implies localization of the process to one organ system, with excellent prognosis. Hand-Schüller-Christian disease represents a relatively chronic, disseminated form of the disease with variable prognosis. Letterer-Siwe disease refers to a subacute or acute disseminated expression of the disease, with poor prognosis.

There are no specific clinical signs of the disease. All but 3 of the 36 patients revealed bone involvement. The skull, orbits, femora, pelvis and ribs were most frequently involved. The roentgenographic findings included: (1) marginal bone sclerosis; (2) expansion of involved bones; (3) sequestration; (4) excessive periosteal new bone formation; (5) rapidly developing lytic lesions; (6) marginal irregularity; (7) vertebral lesions (compression deformity of a vertebral body was a frequent manifestation); and (8) pulmonary manifestations (disseminated nodular infiltrations associated with pulmonary fibrosis and obstructive emphysema).

The roentgenographic features were quite variable and in general the correlation with the histologic findings was poor. The various osseous lesions encountered in this series simulated such conditions as osteomyelitis, Ewing's sarcoma and metastatic neoplasia.

Biopsy is usually necessary for a definitive diagnosis.—*Samuel G. Henderson, M.D.*

NACHEMSON, ALF. *In vivo* discometry in lumbar discs with irregular nucleograms. *Acta orthop.*

scandinav., 1965, 36, 418-434. (From: Biomechanics Laboratory, Department of Orthopaedic Surgery, University of Gothenburg, Sweden.)

Usually lumbar disks are evaluated from standard roentgenograms, including myelograms. However, it has been shown that degenerative changes can exist inside the disk in spite of a normal roentgenogram. Thus special procedures such as disk puncture and diskography have become more common in difficult cases of low back pain.

Diskometry is another special procedure which evaluates the pressure inside the disk. The method is valid only in normal or slightly degenerated disks which still retain some hydrostatic properties. This method was developed in cadavers and confirmed by macroscopic examination.

Extending the method to *in vivo* conditions, 3 groups were found. In the first group, the pressures were the highest and the nukleogram was normal. The second group recorded lower pressures, and the diskogram showed fragmentation of the nucleus and occasional fissure formation in the annulus. The third group had the lowest pressures which were also very variable and nonreproducible. The nukleogram showed marked changes.

The article concerns this second group. The method of diskometry is detailed. Observations in 10 patients are recorded.

Moderate degeneration in lumbar disks seems to lessen the internal stress by about 30 per cent. This degree of degeneration will change the distribution of stress compared to a normal disk so that the vertical load on the dorsal part of the annulus will increase by 100 per cent while the tangential tensile stress in the same part will decrease by 50 per cent. Calculations revealed that in a 70 kg. man, having a moderately degenerated third lumbar disk, the vertical load on the annulus would be 10 kg./cm.² in the 20° forward sitting position. The normal is 5 kg./cm.². The tangential tensile stress on the dorsal part of the third lumbar disk would be 30 kg./cm.² as compared to a normal 60 kg./cm.².—*W. J. Carmony, Jr., M.D.*

MARSHALL, THOMAS R., and WING, HERMAN.

Arteriographic diagnosis of the osteoarthropathies of the hand. *South. M. J.*, Feb., 1966, 59, 135-140. (From: Departments of Radiology and Physical Medicine and Rehabilitation, University of Louisville School of Medicine, Louisville, Ky.)

Arteriographic studies of the hand were carried out in 125 patients after percutaneous injection of the brachial or axillary artery. The brachial artery was preferred. A Sanchez-Perez cassette changer was used and several injections of 10-20 cc. of conray 60 per cent were sometimes needed to obtain good filling. A tourniquet was applied above the needle site

and the needle was pointed toward the shoulder. Premedication included 100 mg. meperidine and 1/150 gr. of atropine. Raynaud's phenomenon, when present, required larger amount of medication, because patients had more pain during the injection.

Twenty-five of the patients studied were normal. In 40 cases of rheumatoid arthritis of the hand, two types of digital lesions were observed. These were the occlusive and hyperemic patterns and in 8 patients there was evidence of both patterns. The occlusive pattern was seen commonly in patients with marked destructive and erosive bone change. The hyperemic pattern was seen in areas of synovial proliferation in a joint or tendon sheath usually near the wrist or carpal bones.

Occlusive patterns were in: hypertrophic osteoarthritis (main type); gouty arthritis; and dermatomyositis. The severity of the occlusive pattern showed a direct relationship to the extent of the disease.

Spastic and occlusive changes were seen in Raynaud's disease, psoriatic arthritis and in lupus erythematosus.

Hyperemic patterns were noted in polyarteritis nodosa in addition to spastic-occlusive patterns in the digital arteries.

It is felt that determination of the extent and severity of organic peripheral vascular disease of the hand by arteriography may be useful in selection of the proper therapeutic management.—*Richard E. Kinzer, M.D.*

BLOOD AND LYMPH SYSTEM

PARKER, JOHN O., CHALLIS, THOMAS W., and WEST, ROXROY O. Selective coronary arteriography. *Canad. M. A. J.*, Feb. 26, 1966, 94, 425-430. (From: Departments of Medicine and Radiology, Kingston General Hospital, and Cardiopulmonary Laboratory, Queen's University, Kingston, Ontario, Canada.)

The authors describe in detail their application of the Sones method of selective coronary arteriography in 255 patients. No deaths and only limited morbidity were encountered. Four episodes of ventricular fibrillation occurred, all of which were successfully treated. Short periods of asystole were relatively common.

Both coronary arteries were directly cannulated in 88 per cent of the entire series, and in 95 per cent of the last 100 cases. The selective injections were made using 6 to 8 cc. hypaque with the patient in right anterior oblique and anteroposterior position, so as to visualize the arteries in 2 projections, utilizing a 35 mm. cine camera.

The authors found the procedure most useful in patients with atypical clinical and electrocardiographic features. Vessels as small as 200 μ in diameter can be demonstrated. No normal coronary arterio-

grams were found in any patient with unequivocal clinical evidence of coronary disease. Frequently normal coronary arteriograms were noted in patients on active therapy. However, coronary arterial occlusion has been seen in patients with normal resting and post exercise electrocardiograms and atypical symptoms.

Coronary arteriography is helpful in preoperative assessment of patients with aortic and mitral valve disease in an age group where coronary disease may be a complicating factor. Also, a precise knowledge of the extent and location of coronary lesions in patients for whom myocardial revascularization procedures are contemplated is essential.

The authors include several single frame cine reproductions to illustrate normal and pathologic coronary arteries.—*W. J. Carmony, Jr., M.D.*

PUYLAERT, C. B. A. J. Fatal and nearly-fatal mesenteric infarction, caused by intramural injection in translumbar biphasic aortography (report of 7 cases and of a useful sign of impending infarction). *J. belge de radiol.*, 1965, 48, 671-695. (Address: Prof. Donderstraat, 73, Tilburg, The Netherlands.)

Intramural injection of contrast material during translumbar aortography with occlusion of the origin of an artery may be responsible for nearly all complications of aortography. This conclusion is based on 600 translumbar and 100 transfemoral aortographies carried out in a 10 year period. The biphasic method of aortography, with a series of roentgenograms of the extremities made first and a pelvic series made second, allows a delayed observation of the area of the injection during the first roentgenograms of the second series, the two injections being made through the same needle.

Much has been written on the complications of aortography. Some still believe that toxicity of contrast material when injected into a small vessel is responsible for necrosis. The author joins a second group of investigators who believe that the true mechanism of necrosis is the intramural injection which in turn obstructs the small vessels, often after the vessel has been filled with contrast material. Prolonged contrast filling of the mesenteric artery and of the colon is the sign of an impending infarction.

Intramural injection of contrast material can give the same occlusion of branches of the aorta as a dissecting aneurysm does. This occlusion occurs after filling of the aorta and its branches with contrast material. Delayed "wash-out" of the mesenteric vessel and prolonged contrast filling of the colonic wall vessels are signs of impending infarction and proper interpretation and attention to the patient can help to save a life.

The Seldinger catheter method will help to avoid some complications, but not all. The kind of con-

trast material used is not significant. Delayed roentgenograms for detection of "trapped material" or retained contrast material will allow a warning signal so that the patient may be watched carefully.

Nine case reports in all are included and an excellent series of well reproduced roentgenograms illustrates each one.—*Richard E. Kinzer, M.D.*

CHUDÁČEK, Z. Splenoportography in Budd-Chiari's syndrome and disease. *Radiol. clin. et biol.*, 1965, 34, 247-253. (From: Roentgen-diagnostic Department, University Hospital, Plzeň, Czechoslovakia.)

The author reports 3 cases of Budd-Chiari's syndrome in which splenoportography was performed.

He believes that in the early stages, the roentgen signs are typical. The liver is seen to be markedly enlarged. Contrast material fills the liver well, with the peripheral branches visualized and all branches seen to be somewhat dilated. The filling persists for a long time. The splenoportal vessels are dilated and have a tortuous course.

In the later stages of the disease the roentgenographic appearance is similar to that of advanced cirrhosis.—*G. L. Sackett Jr., M.D.*

SAYEGH, E., BROOKS, T., SACHER, E., and BUSCH, F. Lymphangiography of the retroperitoneal lymph nodes through the inguinal route. *J. Urol.*, Jan., 1966, 95, 102-107. (From: United States Naval Hospitals, Portsmouth, Va., and San Diego, Calif.)

The inguinal canal and the spermatic cord are exposed by surgical approach. One cc. of Evans blue dye is injected beneath the tunica albuginea except in those patients who have testicular neoplasms. In the latter instance, a rubber-shod clamp is applied to the cord at the internal ring and the dye is injected in the fold between the testicle and epididymis under the visceral layer of the tunica vaginalis. After identification of the relatively large lymphatic channel, it is cannulated by a $3\frac{1}{2}$ plastic or ureteral catheter. This catheter is tied in place and brought out from the lower angle of the wound. Following closure, the ethiodol is injected outside of the operating room at a rate of 0.5 cc. per hour; 3 cc. is usually quite adequate for the demonstration of the retroperitoneal lymphatics. Films are exposed at intervals of 2, 12, 24, and 48 hours. The catheter is usually left in place and further injection may be continued after the 48 hour exposure if necessary.

In normal subjects there are 4 to 8 lymphatic vessels anastomosing freely at both their proximal and distal ends. These vessels may turn abruptly anywhere from L4 to L2. A small sentinel lymph node best seen in the lateral view is identified during the early portion of the injection and before the main

lateral lymph nodes are visible. On the left side, the lymph nodes at the L1-L2 level are the first to be filled followed by retrograde filling of those at the level of L3-L4, D12 and the thoracic duct. On the right side, the flow runs directly to the left lateral lymph nodes as visualization of the right superior and right inferior lateral lymph nodes becomes apparent. In comparison with the immediate crossing of the right lymphatic channels to the contralateral side, those on the left side cross over only after the primary relays are filled and stasis drives the ethiodol through the collateral routes. Only in those patients who have had previous surgical procedures involving the pelvic lymphatics does one see direct testicular lymphatic drainage to the iliac and inguinal lymph nodes.

The interpretation of the films is often difficult. Evidence of massive displacement of the primary lymphatics or early filling of collateral vessels without filling of the primary lymph nodes may be seen. Various types of defects involving normal-sized lymph nodes or enlargement of lymph nodes with or without radiolucent defects may indicate evidence of tumor involvement. On the whole, the early diagnosis of cancer metastasis by this method has been disappointing. Advanced metastasis is relatively easy to diagnose and might be helpful in the surgical or radiotherapy approach to the treatment of these lesions. Negative signs and seemingly normal lymphangiograms may be misleading. In certain instances, there is an advantage in combining inferior vena cavography with lymphangiography.

The treatment of lymphomas by the intralymphatic injection of radioisotopes and chemotherapeutic agents has been attempted without success. It is possible that the inguinal route of injection of such cancericidal drugs might improve the results of this type of treatment.

The authors use 7 composite figures showing the

surgical technique and the radiographic findings resulting from this procedure.—*George W. Chamberlin, M.D.*

REDMAN, HELEN C. Dermatitis as a complication of lymphangiography. *Radiology*, Feb., 1966, 86, 323-326. (From: Department of Radiology, Stanford University School of Medicine, Palo Alto, Calif.)

Dermatitis as a complication of lymphangiography has not yet been described in the literature, although wound infections, lymphangitis, and swollen extremities have been noted. The author reports 4 cases of severe dermatitis in a series of 400 lymphangiographic studies performed in the Stanford University Department of Radiology. Three cases are reported in detail. The technique employed has been described elsewhere.

In all 3 cases reported, extravasation of ethiodol had occurred but there were other cases with extravasation which did not manifest a dermatitis. This dermatitis developed 1-3 weeks following injection and was characterized by confluent erythema, swelling, and rather severe discomfort. Its location was found to overlie the extravasated medium and major lymphatic pathways, and an associated lymphangitis was apparent in at least 1 case. In each case bacteriologic cultures were negative and administration of antibiotics was apparently noncontributory. Furthermore, dermatologic evaluation supported the diagnosis of local drug reaction of the vascular type.

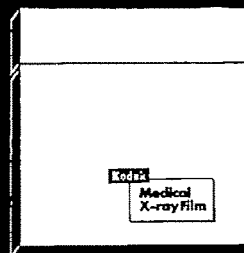
In each case, complete recovery occurred in 2-3 weeks, and the author concluded that symptomatic therapy alone would have been adequate. Specific therapy is not available, although the use of a topical corticosteroid preparation markedly accelerated the recovery in 1 case.—*John Bond, M.D.*



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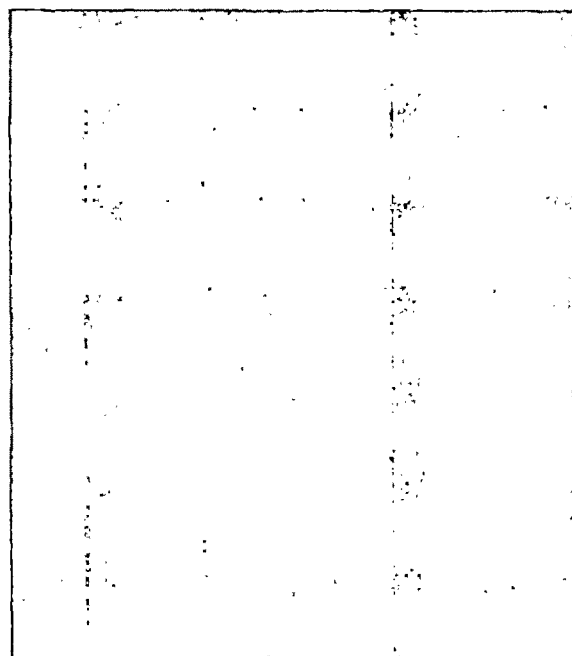


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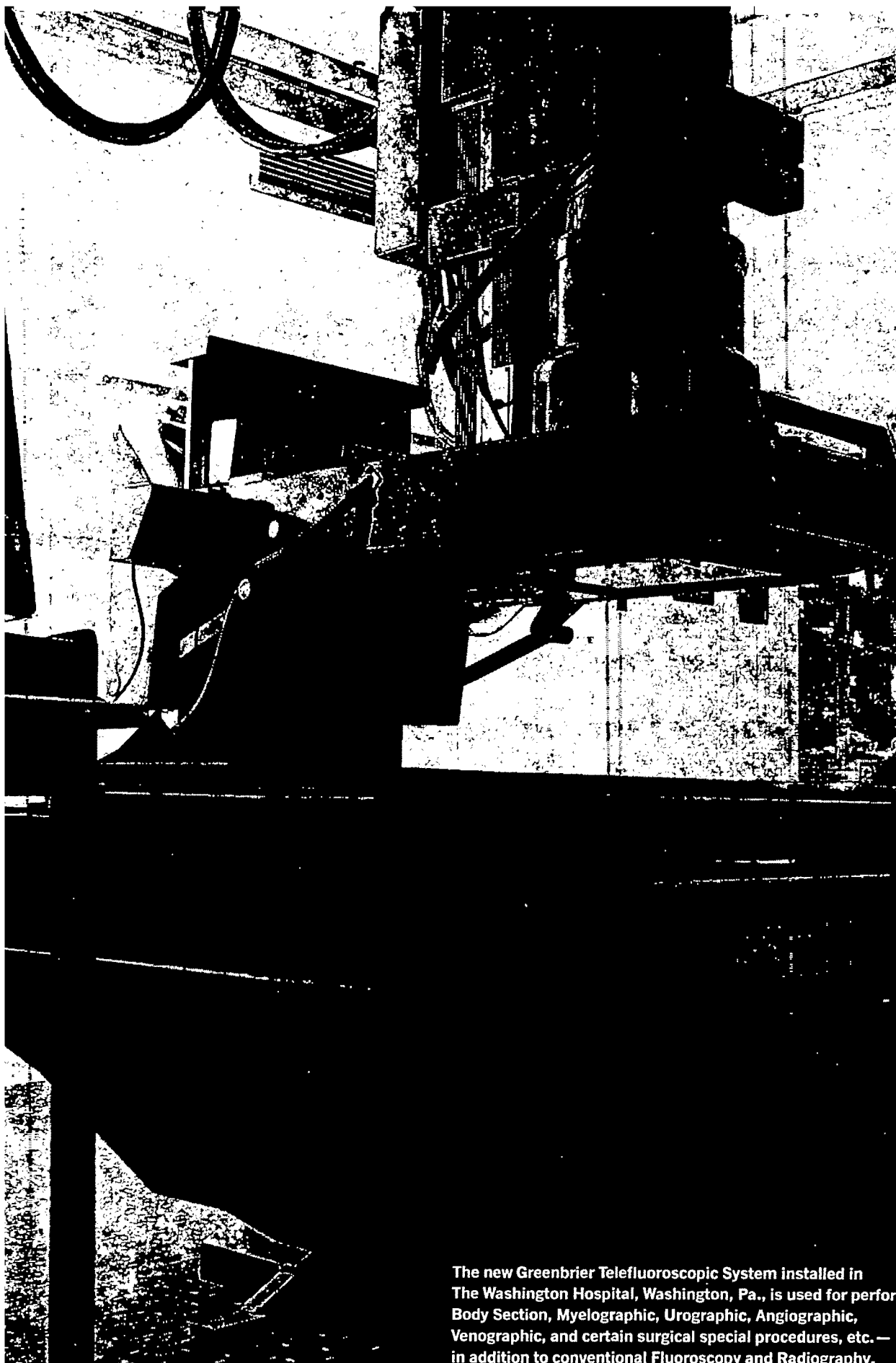
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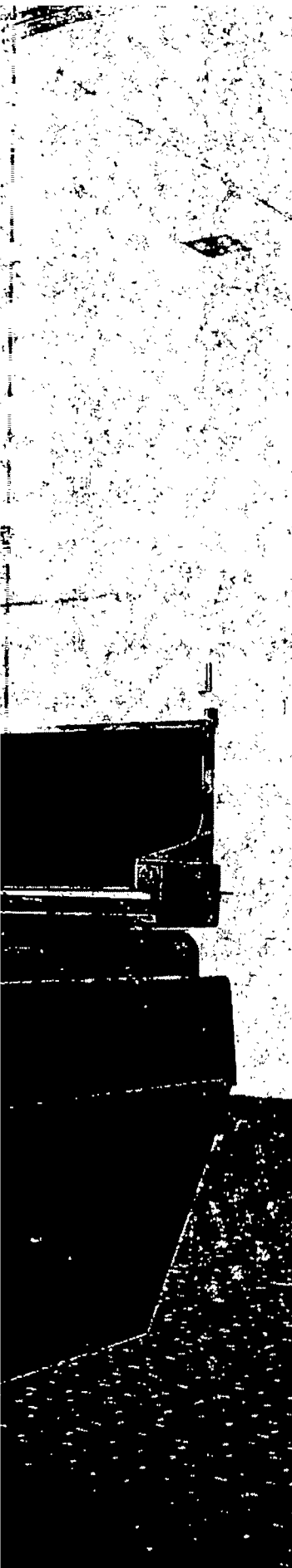
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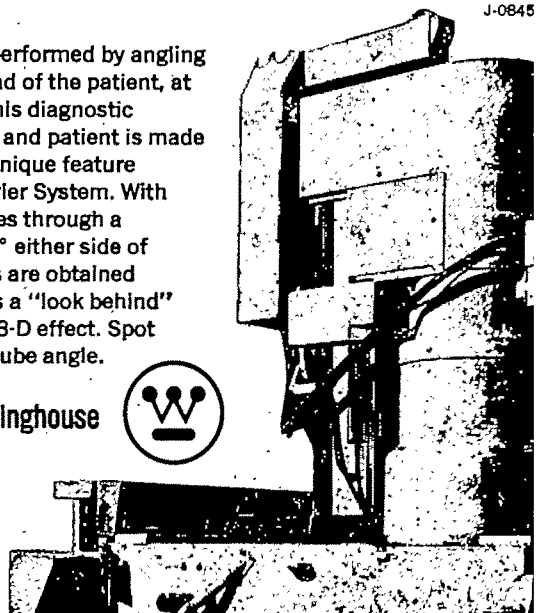
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- **THE TRAIL OF THE INVISIBLE LIGHT: From X-Strahlen to Radio(bio)logy** by E. R. N. Grigg, *Cook County Hosp., Chicago.* '65, 1,016 pp. (8½ × 11), 1,404 figs., (Amer. Lec. Roentgen Diagnosis), \$36.75
- **THE USE OF DIAGNOSTIC ULTRASOUND IN BRAIN DISORDERS** by Charles C. Grossman, *Presbyterian-University Hospital, Pittsburgh.* Feb. '66, 172 pp., 146 il., \$9.00
- **THE EARLY RADIOLOGICAL DIAGNOSIS OF DISEASES OF THE PANCREAS AND AMPULLA OF VATER: Elective Exploration of the Ampulla of Vater and the Head of the Pancreas by Hypotonic Duodenography** by Paul Jacquemet, *Lyon Faculty of Medicine, France; Domingo Liotta, Baylor Univ., Houston; and Pierre Mallet-Guy, Lyon Faculty of Medicine.* Translated by Lee D. Cady, *Baylor Univ.* '65, 256 pp. (7 × 10), 392 il., \$14.50
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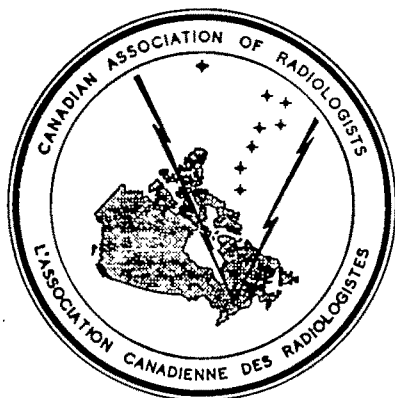
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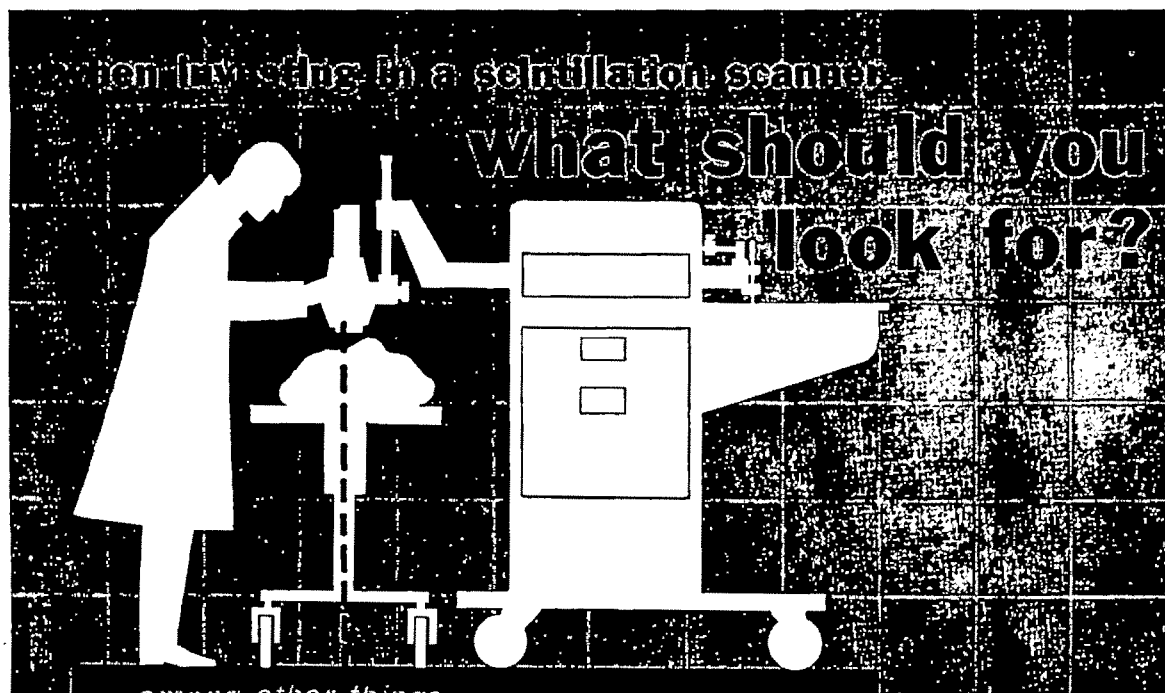
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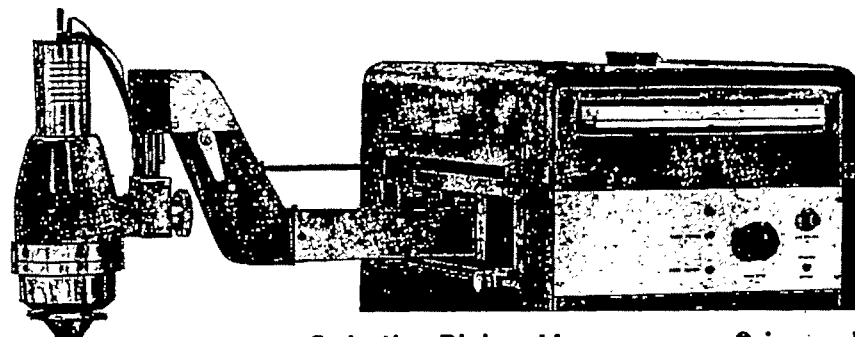
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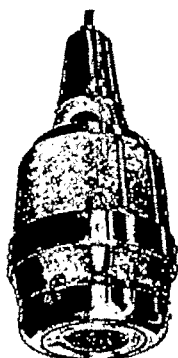
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Advances in Tuberculosis Research

Vol. 15

Edited by

H. BIRKHÄUSER, Basel; H. BLOCH, Basel; C. CANETTI, Paris

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N. W. HORNE, Edinburgh: A Critical Evaluation of Corticosteroids in Tuberculosis

A. M. LOWELL, Atlanta, Ga.: A View of Tuberculosis Morbidity and Mortality Fifteen Years after the Advent of the Chemotherapeutic Era, 1947-1962

A. DEBEAUMONT, Berck Plage: Bactériologie de la tuberculose ostéoarticulaire sous chimiothérapie

H. H. KLEEGER, Onderstepoort (South Africa): Chemotherapy and Chemoprophylaxis of Tuberculosis in Cattle

Vol. 15 of "Advances in Tuberculosis Research" contains four important contributions of vastly different aspects.

The first paper is an extensive, critical evaluation by N. W. HORNE on the effects of the corticosteroid therapy in tuberculosis which is still rather controversial. Then follows a world-wide analysis by A. M. LOWELL on the evolution in the morbidity and mortality rates of tuberculosis during the first and the last seven years of the chemotherapeutic era. The statistical evidence which has been compiled and confronted is impressive.

A. DEBEAUMONT reviews the bacteriological aspects of bone and joint tuberculosis under chemotherapeutical treatment, adding his personal experiences which are valuable from a bacteriological as well as from a pharmaco-dynamic point of view: the dosages of isoniazid and streptomycin for injections within the lesion given by the author will be of the greatest interest to all concerned with therapeutical questions in tuberculosis.

Finally, H. H. KLEEGER reports on chemotherapy and chemoprophylaxis with isoniazid in bovine tuberculosis. This contribution is a proper monograph which, after a detailed analysis of world literature, compiles for the first time the numerous investigations made by the author. The differences and the similarities in bovine tuberculosis as compared with human tuberculosis are of exceptional interest. Not only the veterinarian but also the physician and the epidemiologist will find ample material for reflection.

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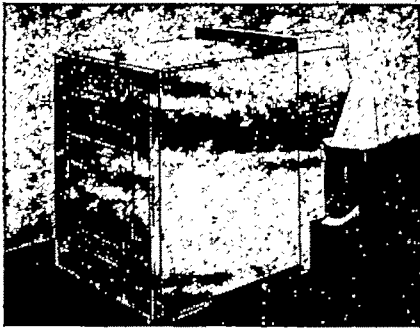
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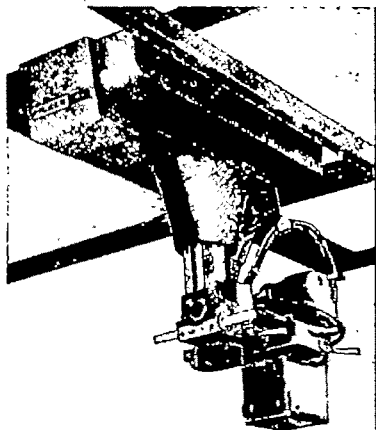
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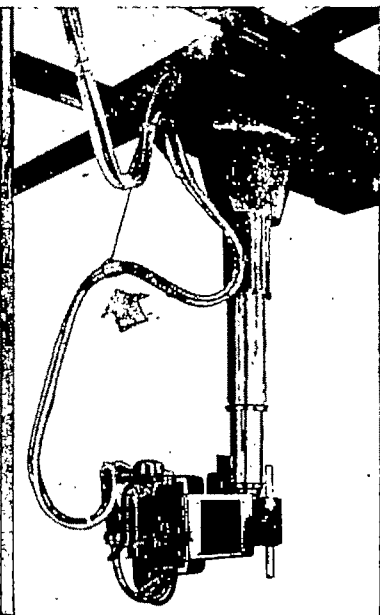
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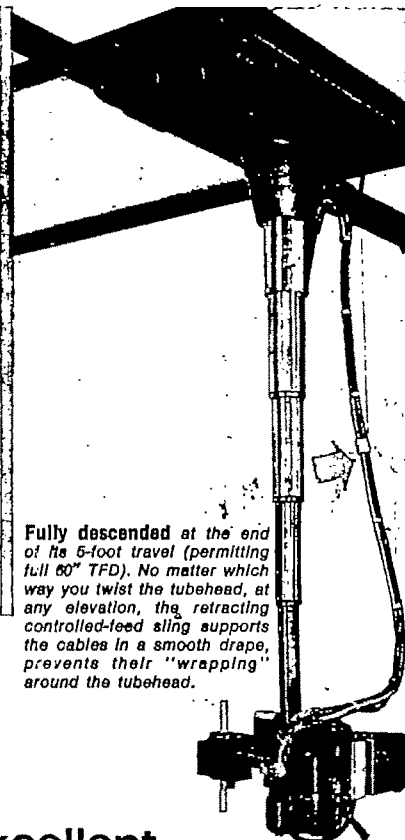
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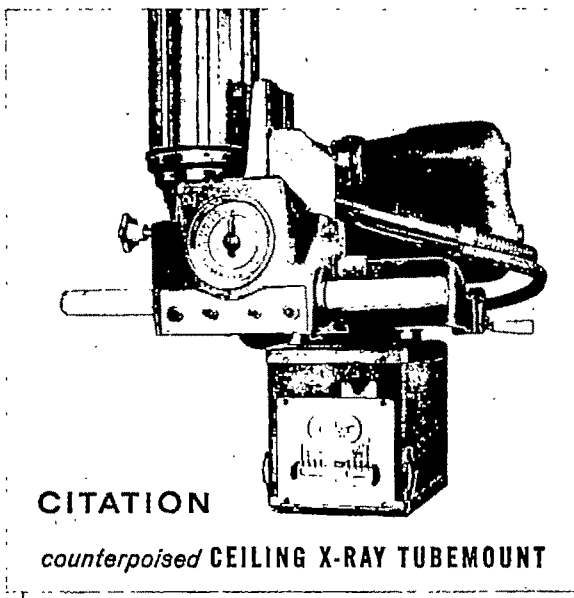


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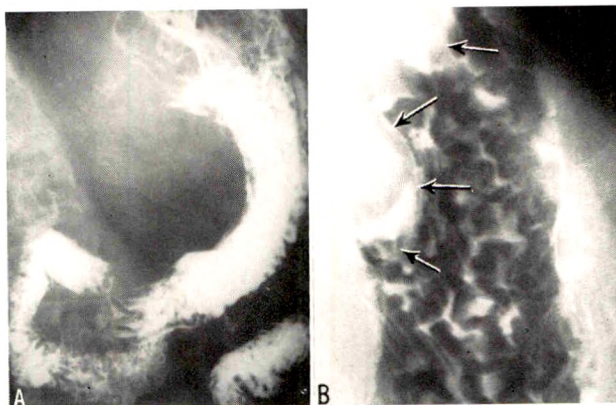


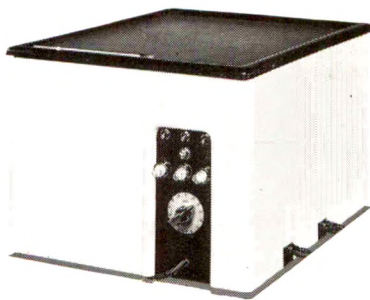
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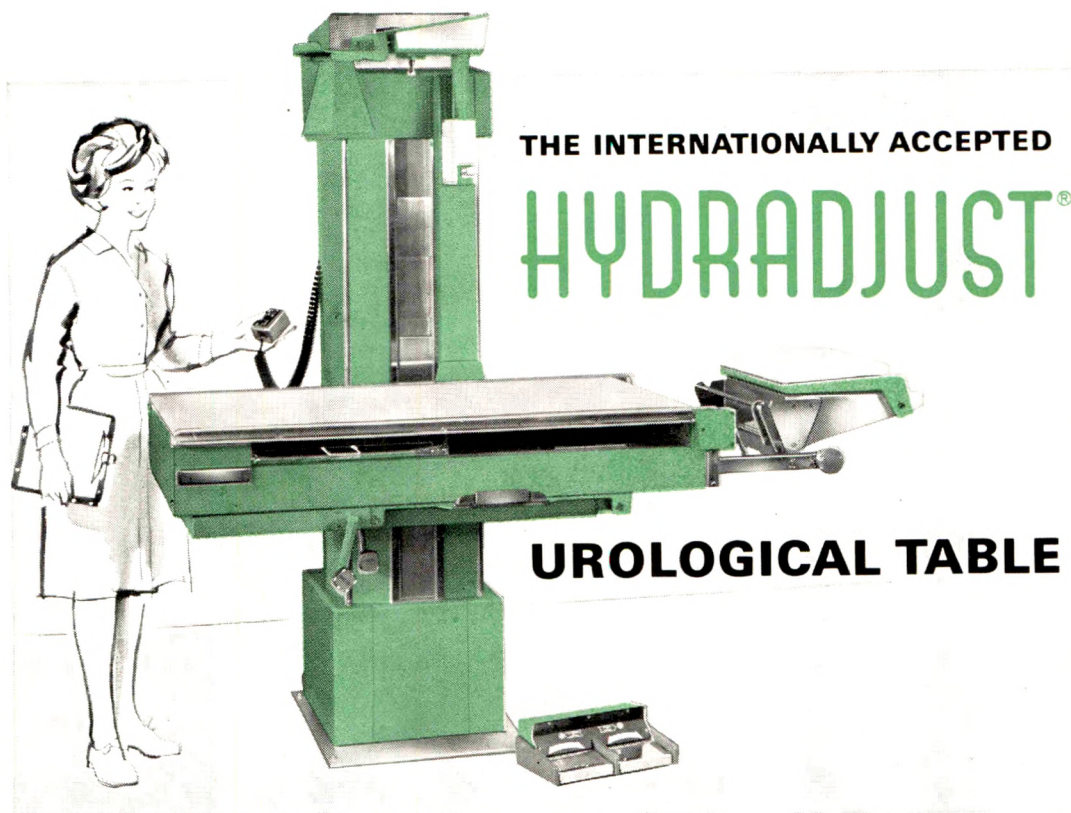
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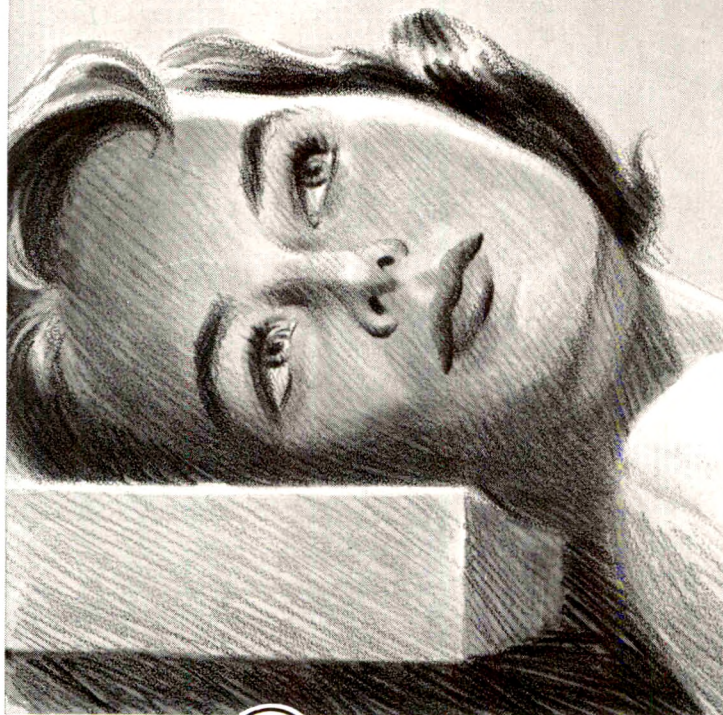
A DIVISION OF RITTER PFAUDLER CORPORATION

CINCINNATI, OHIO 45215

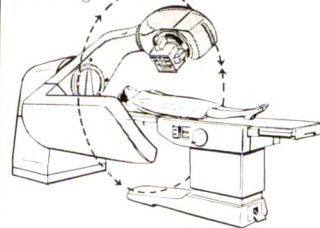
THE *COMFORT* OF THE PATIENT IS IMPORTANT TOO!

Design features of the **THERATRON** 60 and 80

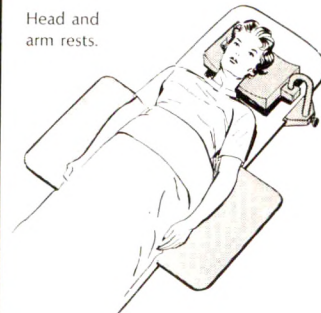
COBALT 60 TELETHERAPY UNITS ensure the maximum physical and mental comfort of the patient, due to the rapid setup time and reduced treatment periods made possible by these units.



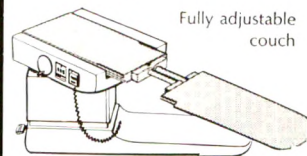
Rotary, fixed beam
or arcing.



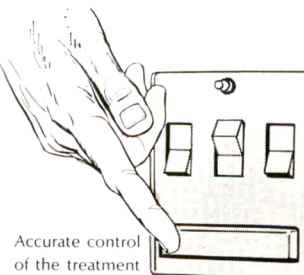
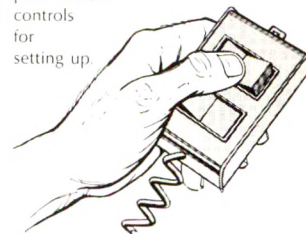
Head and
arm rests.



Fully adjustable
couch



Easy,
push-button
controls
for
setting up.



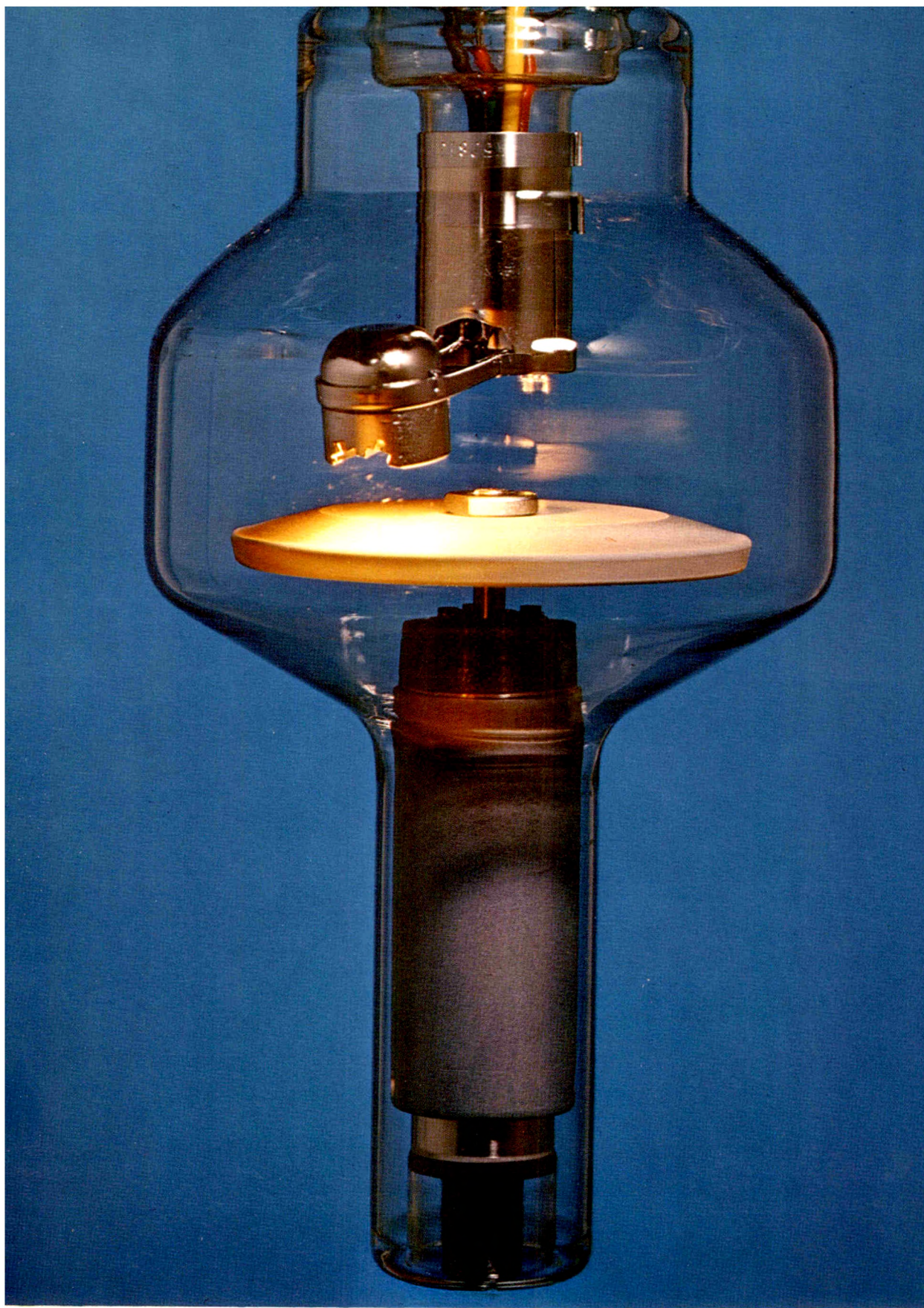
Accurate control
of the treatment



ATOMIC ENERGY OF CANADA LIMITED

Commercial Products • P.O. Box 93 • Ottawa • Canada

64-5M

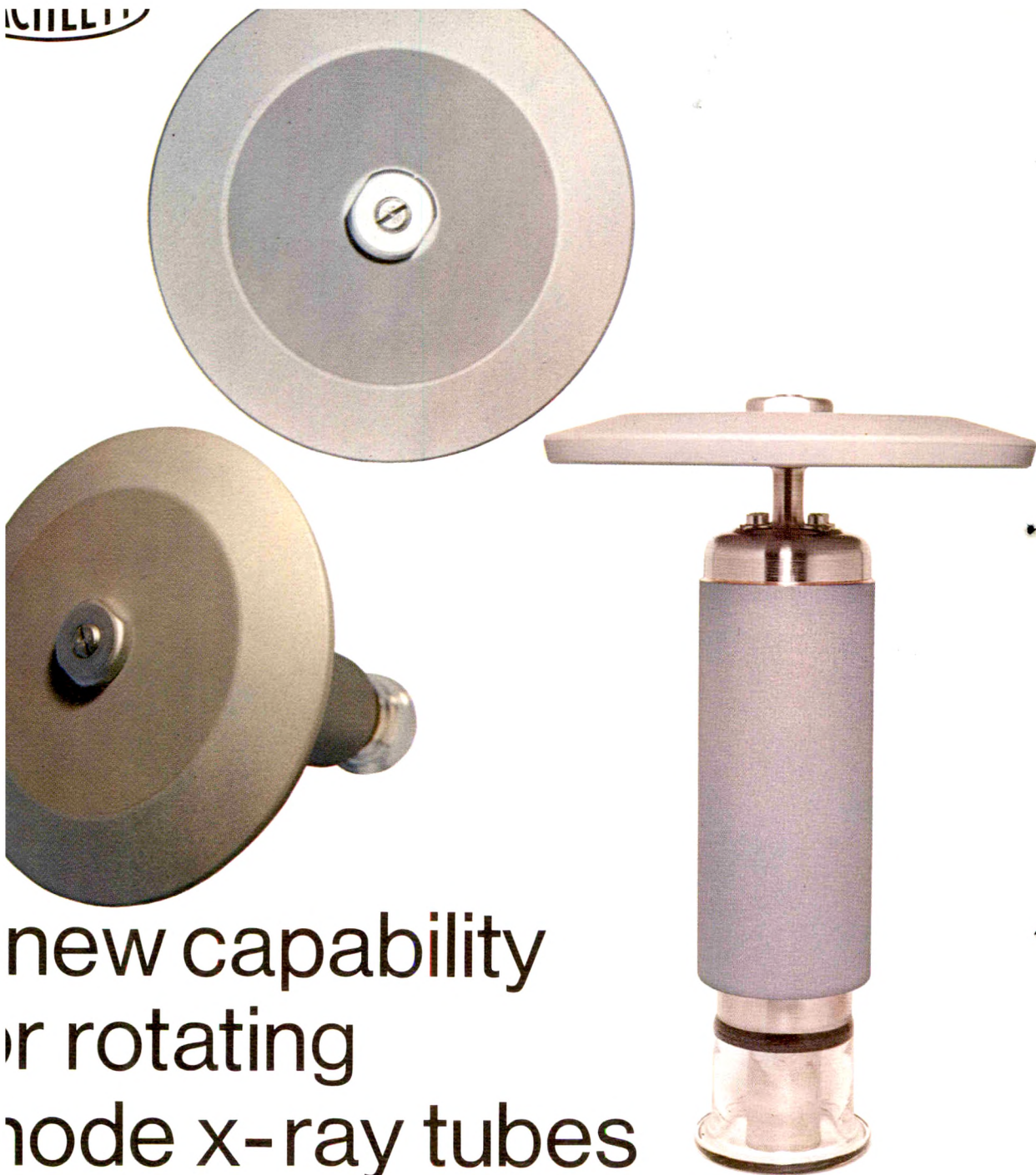


THE MACHLETT DYNAMAX "60"

represents a refinement of the rotating anode X-ray tube concept and a new enlargement of its potential function.

MACH

MACHLETT



new capability for rotating anode x-ray tubes

The new compound target of the Dynamax "60" optimizes mass and heat storage capacity. A strong relatively light metal of superior "heat storage" characteristics is bonded to the heavier tungsten, whose ability to withstand thermal loading remains unsurpassed. The resulting target reduces bearing load, is quicker to obtain full operating speed, and improves high-speed operating life. At the same time, it increases heat storage capacity to extend the operating range of the tube. By comparison, the Dynamax "40" anode heat storage is 110,000 HU; the Dynamax "50", 140,000 HU; and the Dynamax "60", 200,000 HU.

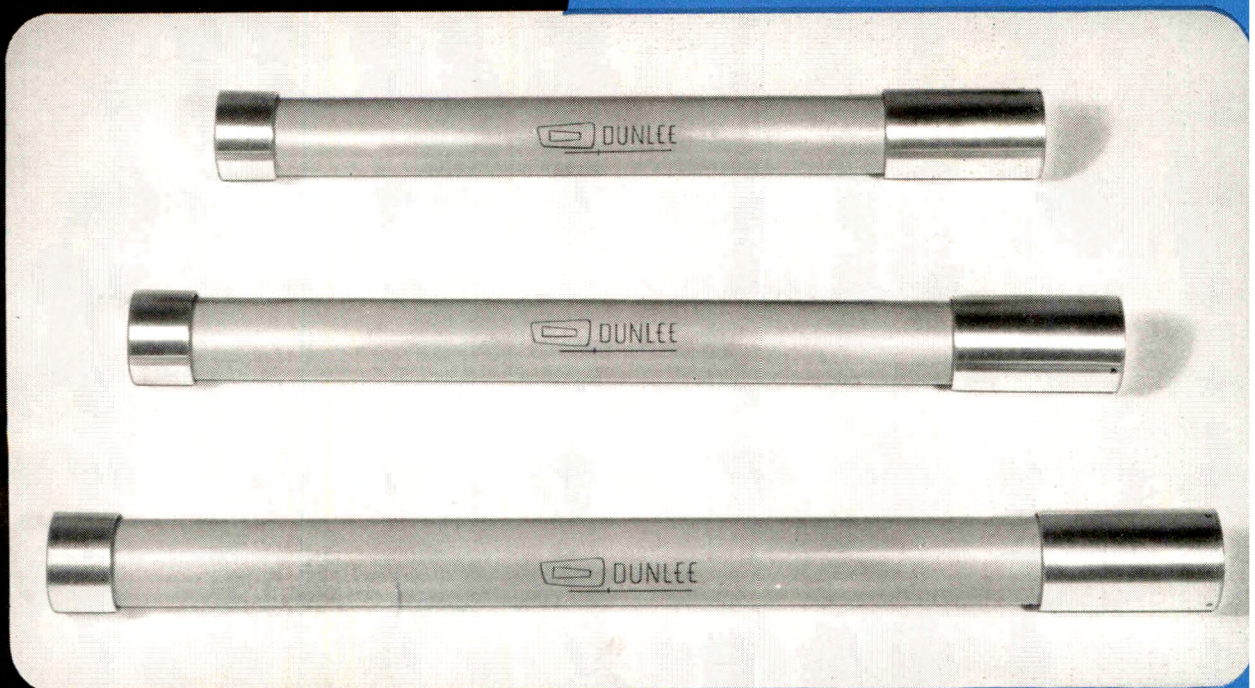
The Dynamax "60" is particularly well-suited for use in modern high-energy equipments of all types. Write The Machlett Laboratories, Inc., Springdale, Conn. 06879.

RAYTHEON

THE MACHLETT LABORATORIES, INC.

A SUBSIDIARY OF RAYTHEON COMPANY

MODERNIZE your X-ray equipment



with
these
NEW

DUNLEE

SDV RECTIFIERS

Maximum Peak Inverse Ratings

SDV-100	100 KvP
SDV-125	125 KvP
SDV-150	150 KvP

Maximum Average Load Current

1/10 sec.	1000 Ma
2 sec.	600 Ma
Continuous	100 Ma

*Consult your x-ray
Dealer or write*

These Dunlee SDV rectifiers are hermetically sealed high voltage silicon units designed for use in your present x-ray generators. They can be used as direct replacements of the hot cathode vacuum rectifiers . . . they provide longer life, in most cases as long as the original x-ray equipment lasts . . . they operate with greater efficiency and low forward drop . . . and they are higher in mechanical strength. Simple and safer to operate, these silicon rectifier cartridges are available in **new** units from the manufacturer of your equipment . . . just ask for them when you buy your next x-ray unit. Use as replacement for your present valve tubes as well.

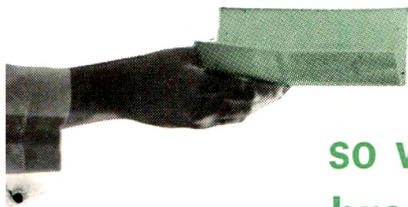


CORPORATION

DEPT. B 1023 S. PUSHECK RD. • BELLWOOD, ILLINOIS
Telephones: Bellwood: LInden 7-9535 • Chicago: COLumbus 1-6931

**Du Pont
focuses
its science
and energy
on
Diagnostic
Clarity**





so we are helping your technologists break a complex problem into bits.

After analyzing most of the available literature, and talking to many radiologists, our scientists concluded that present systems of technic conversion were:

1. difficult for technicians to use
2. not accurate enough
3. not flexible enough

In fact, they often provided a barrier that prevented the technologist from giving the radiologist all of the quality we put into CRONEX*.

So we broke the technic barrier with the Du Pont bit system.

Where other systems rely on formulas, factors, and percentages, our bit system involves only simple addition and subtraction.

With it, your technologists can more carefully duplicate results at different exposures. Or, they can change exposure on small increments to get a predetermined variation in density or contrast.

The Du Pont bit system was created to help you see clearly all that CRONEX is capable of recording. But like most Du Pont innovations, it has the potential of a side benefit. We think it will also help make the job of teaching new radiologic technologists easier and faster than ever.

For an explanation of the Du Pont bit system, and a free chart of variables in bit form, write Du Pont CRONEX X-ray Products, Room 2424, Wilmington, Delaware 19898.

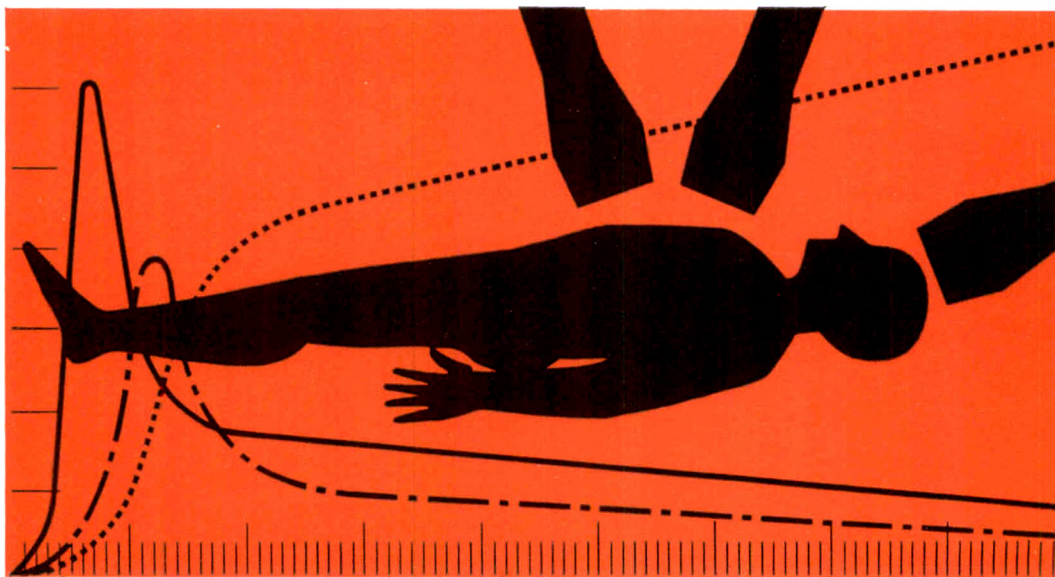
*Du Pont's registered trademark for its medical X-ray film.

CRONEX X-ray Products



Better Things for Better Living
... through Chemistry

Dynamic clinical studies using radioisotopes:



**Are you interested but
don't know quite where to start?**

Then start here.

First let us admit that the dynamic clinical techniques which use radioisotopes for studying various bodily functions are more complicated than well counting or even scanning procedures. Undeniable.

But these methods are valuable, providing either confirmatory clinical data or, in some instances, information which just cannot be obtained by any other means. Long-established applications of these techniques include, for example, renal function studies, cardiac output determinations and hepatic function assessment. Or perhaps the newer techniques such as cerebral blood flow or pulmonary function would be of interest.

Whatever your interest, we can minimize the technical difficulties of getting into this field.

Our offer: to work with you in any and every way to make your entry into this area as painless as possible. Specifically, we would be

happy to talk with you about these methods, to provide the necessary information on existing procedures, to help you plan your radio-tracer studies, to assist in interpreting results, and to aid in the training of your staff in all phases of radioisotope dynamic function methodology. Or, to work with you in any other way that you may wish. With no obligation.

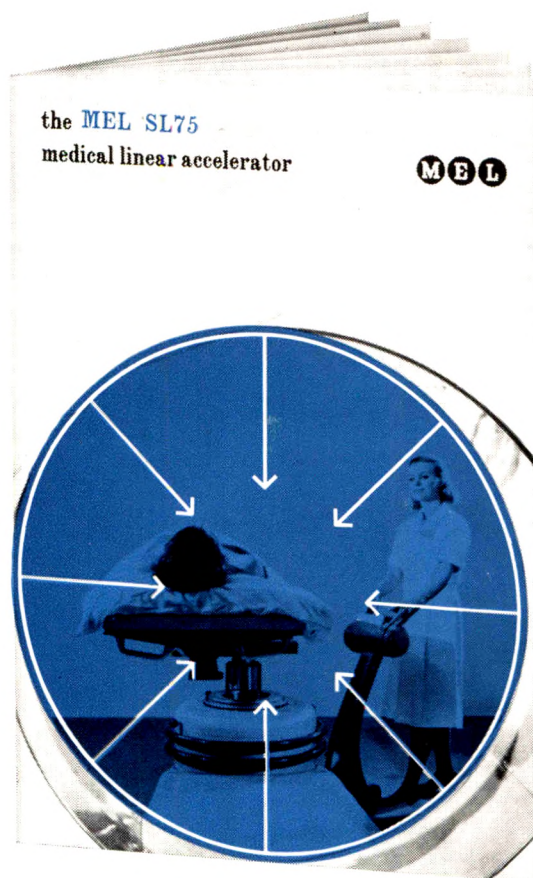
Then it will come as no surprise that we can also help you select the equipment that makes sense for your needs. And to begin with, this can be a relatively simple outfit; your first commitment can be limited to the basic equipment since refinements can be added easily as needed. You should also know that our line of instruments for dynamic function work of every kind is unmatched in diversity or quality.

So, an invitation: start a dialogue by requesting our new brochure DCAR6.

Picker Nuclear: 1275 Mamaroneck Avenue, White Plains, New York 10605



**In one page we couldn't outline
all the important features of the
M.E.L. SL75 linear accelerator**



so we offer this book

17 years of practical experience has gone into the M.E.L. SL75, an advanced, reliable, precision engineered linear accelerator now in use throughout the world. But it will take you only a few minutes to write for the free booklet.



The M.E.L. Equipment Company Ltd., Manor Royal, Crawley, Sussex, England.

This equipment is sold in the USA through
NORTH AMERICAN PHILIPS CO INC
100 East 42nd Street New York 17 NY



CYSTOKON

the first contrast medium
'tailor-made'
for CYSTOGRAPHY

all you add is the infusion set.

- premixed—no powders to measure, no media to mix and dilute
- presterilized—no bottles to clean, sterilize or autoclave
- easily administered by gravity flow or other instillation techniques
- new screw-cap bottles—readily adaptable to venoclysis sets



CYSTOKONTM

(SODIUM ACETRIZOATE 30%)

Unsurpassed as a safe, efficient, economical contrast agent

Well tolerated by urinary tract mucosa ■ High iodine content for maximum contrast with minimum salt concentration ■ Rapidly diffused in the urine for homogeneous opacification ■ No waste—30-50% lower cost than comparable quantities of other commonly employed agents

Three bottle sizes for more flexible dosage and volume ranges

250 ml. single-dose, disposable bottle (shown at left) ready to use full strength for most cases

500 ml. dilution-unit bottle holding 250 ml. Cystokon ready for dilution to desired concentrations from 30% to 15%

100 ml. multiple-dose vial to provide further concentration and volume flexibility

Caution: Not for intravascular administration

Description: Cystokon is a sterile aqueous solution containing 30% w/v of the sodium salt of 3-acetamido-2,4,6-triiodobenzoic acid. Each ml. contains 0.3 Gm. sodium acetrizoate (0.2 Gm. iodine), not more than 0.05 mg. calcium disodium ethylenediaminetetraacetate as a stabilizer, and not more than 0.15 mg. sodium phosphate as a buffer. The pH of the solution is adjusted to within 7.0 to 7.4. Since the solution itself will not support bacterial growth, additional bacteriostatic agents have not been added. The solution is somewhat sensitive to light and must be protected from strong daylight or direct exposure to the sun.

Clinical Application: Cystokon is prepared and packaged specifically for cystography and retrograde pyelography. It may be employed in simple retrograde cystography and pyelography, voiding cystourethrography, delayed cystography and other appropriate modifications of these techniques.

Contraindications and Side Effects: No evidence of irritation or toxicity to the urinary tract mucosa has been reported with Cystokon. However, minor side reactions associated with the procedure, e.g., nausea, vomiting, pain, salivation and sweating, may be encountered in rare instances. Certain pathologic conditions may, in the judgment of the attending physician, contraindicate retrograde pyelography and cystography.

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Pharmaceuticals
LINKING CHEMISTRY TO MEDICINE[®]

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MALLINCKRODT CHEMICAL WORKS
St. Louis, Missouri 63160

STILL SHORTER EXPOSURES from RÄDELIN

RÄDELIN TYPE STF-2 SCREENS are 30% faster than currently available high speed screens . . . effective throughout the entire useful radiographic range (45 to 160 KvP).

8 lines/mm resolving power makes Type STF-2 ideal for portable, roll film, and spot film techniques and wherever shortest possible exposures are indicated.



Radelin Type STF-2 is one of Radelin's new Maximum Resolution Series screens designed to provide greater resolution-to-speed ratios than ever. Other available types are: Type T-2 (medium-speed), 12 lines/mm; Type TF-2 (high-speed), 10 lines/mm; Type UD (ultra-detail), 14 lines/mm.

Consult your Radelin dealer today . . . for X-ray screens that provide the best performance science has produced.

RÄDELIN DIVISION



UNITED STATES RADIUM CORPORATION

MORRISTOWN, N. J. Offices: Chicago, Ill. and North Hollywood, Calif. Subsidiary: Radelin Ltd., Cooksville, Ont., Canada. Affiliate: U.S. Radium Corp. (Europe), Geneva, Switzerland.

Visit us at the American Roentgen Ray Society Meeting—Booth #46



Now...a new standard of excellence in X-ray film performance!

The Red Seal X-ray film being supplied today is made with an entirely new and highly efficient emulsion...the first of many new developments to come from Ilford in the months ahead.

New Red Seal is a high speed, fine grain film with excellent resolving power, resulting in minimum exposures and sharp, clean images of outstanding contrast. Fog level is at an absolute minimum. The film works satisfactorily throughout the entire range of kVs, up to the highest in current use, and processes well in all types of automatic machines.

Your regular X-ray supplier has the new Red Seal for immediate shipment in 300 and 500 sheet economy bulk packings designed exclusively for the American market.

We invite a trial of this exceptional product.

MADE IN THE BRITISH TRADITION FOR QUALITY



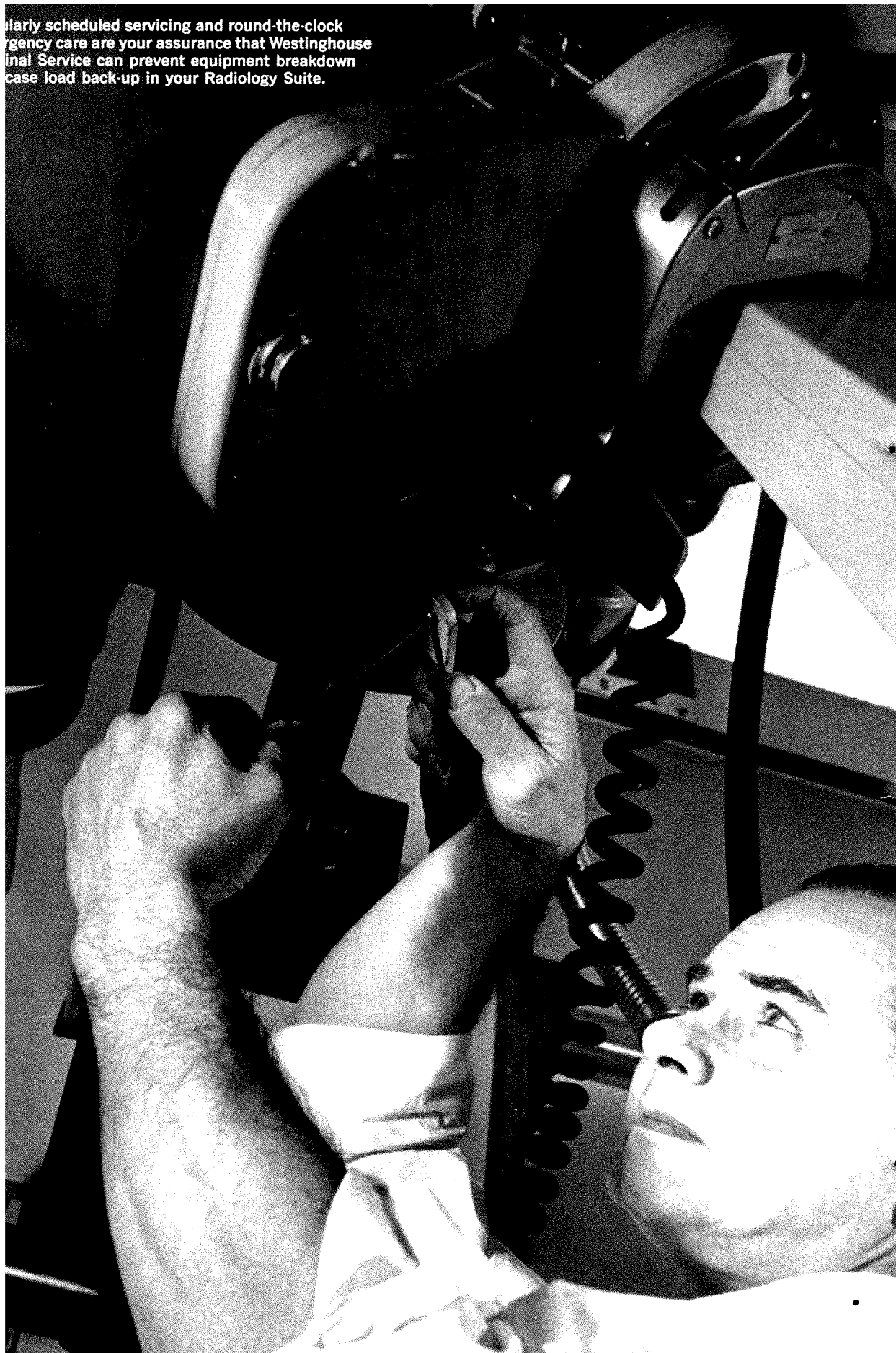
New Bulk Pack Cartons!

The 300 sheet (folder wrapped) and 500 sheet (non-interleaved) economy packings of Red Seal are shipped in distinctive maroon cartons featuring a convenient lift-tape.

Also available in 75 and 25 sheet cartons, folder wrapped, in all popular sizes.

ILFORD INC. 37 WEST 65TH STREET, NEW YORK, N.Y. 10023

larly scheduled servicing and round-the-clock
rgency care are your assurance that Westinghouse
inal Service can prevent equipment breakdown
case load back-up in your Radiology Suite.



Westinghouse planned equipment protection keeps your X-Ray Department in continuous operation.

Westinghouse Sentinal Service™ is a complete X-Ray equipment care service. It's designed to keep your Radiology Department operating without costly interruptions—and tailored to your budget.

With one moderate, budgeted business expense you protect the life and reliability of your equipment. You head off the critical problems of case load back-up. And you rid yourself of the responsibility for equipment maintenance.

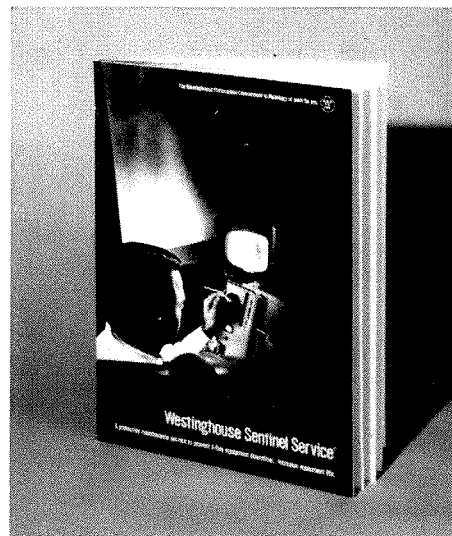
Westinghouse Sentinal Service gives you a planned protection program that features regularly scheduled equipment inspection and care.

Emergency repair, too—if necessary. Even the costs of parts and labor may be included. Send for our free booklet. Westinghouse X-Ray Division, 2519 Wilkens Ave., Baltimore, Md. 21203. J-08457

You can be sure if it's Westinghouse



The complexity of a modern Radiographic and Fluoroscopic System demands the attention of men with the highest degree of technological skill. Westinghouse Service Specialists are trained to maintain and repair today's most sophisticated equipment.



We'll be glad to send you a free copy of our new booklet "Westinghouse Sentinal Service," with detailed information about our planned program of equipment care. Write us, without obligation: Westinghouse X-Ray Division, 2519 Wilkens Avenue, Baltimore, Md.

The Westinghouse Professional Commitment to Radiology at work for you

Diagnosis by ultrasound.

(Would you like to know more about it?)

Because ultrasonic diagnosis is now maturing into a highly useful technique in several areas of medicine, and because reliable ultrasonic equipment is now available for routine use, and because ultrasonic diagnosis can often complement and confirm radiological diagnosis (and can sometimes even do that which x-ray methods cannot do safely *or at all*), Picker X-Ray has joined forces with Physionic Engineering, Inc., a pioneer in the ultrasonic field, to provide ultrasonic equipment to the medical profession. What does this mean to you? It means that the Picker organization, with its commitment to the satisfaction of its customers, is now able to serve you in this new field.

To this end, the coupon below is an invitation to you to learn more about diagnosis by ultrasound and/or our ultrasonic diagnostic equipment.



Picker X-Ray Corporation
1275 Mamaroneck Avenue
White Plains, New York 10605

I've checked the items below that interest me:

- ☐ General information about diagnosis by ultrasound.
- ☐ Bibliography of references to the use of ultrasonic diagnosis in my field.

.....
(Please indicate specialty)

- ☐ List of textbooks and general articles on ultrasonic diagnosis.
- ☐ Information on ultrasonic equipment.
- ☐ I would be interested in a demonstration of this equipment.

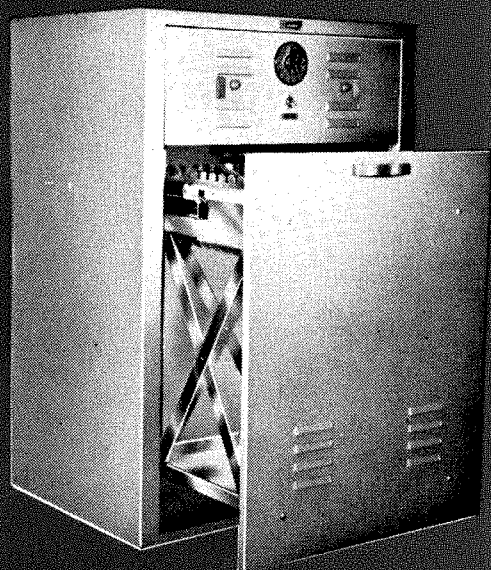
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INSTITUTION

ADDRESS

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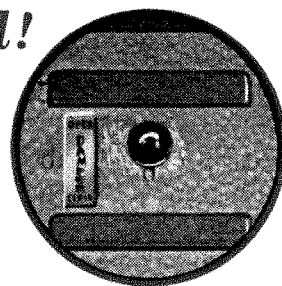
**What's so special
about Halsey
Film Dryers?... the climate compensato
control!**



Model No. 600-D



Model No. 601-D



The biggest bugaboo of film dryers is humidity the darkroom . . . environmental moisture which turns the most efficient unit into a sluggish, slow acting flop.

Now HALSEY introduces the *climate compensator* — a system of air control that lets you shut out outside humidity when it's too high . . . or bring in outside air when it's cool and dry.

The result . . . faster film drying — regardless of climate conditions!

No. 600-D. Fatigue-free loading from the top. Handles 12 films every 20 minutes. Complete with automatic timer — a guard against fire hazard due to failure to turn off the heater. Dimensions: 23" wide, 33" high, 17½" deep.

No. 601-D. Economy version of above — loads from the front. Recommended for stacking on top of No. 600-D for stoop-free loading, when extra capacity is desired. Dimensions: 23" wide, 33" high, 17½" deep. Automatic Timer (No. 602-DT) available.

No. 601-D-H. For restricted space — similar to No. 601-D, but almost 10" narrower; accommodates 6 film. Dimensions: 13½" wide, 33" high, 17½" deep.

Write for detailed literature



HALSEY X-RAY PRODUCTS, INC.
1425-37th STREET, BROOKLYN, N.Y. 1121

CHICAGO: 7321 Monticello Avenue, Skokie, Illinois 6007
LOS ANGELES: 1816 W. 8th St., Los Angeles, Calif. 9001

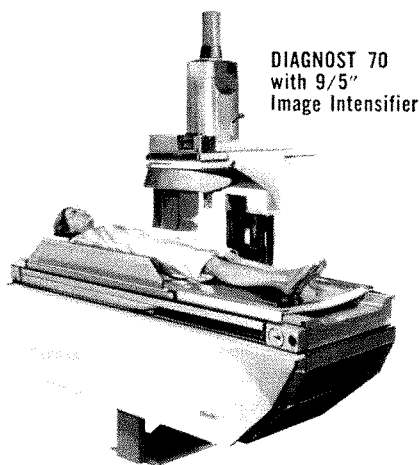
Success hasn't spoiled NORELCO

Based on their quality radiographic and fluoroscopic performance, Norelco Image Intensifier Systems consistently lead the field. Compare results, compactness, stability, longevity and simplicity of operation with other systems. You will find no match for the Norelco 6" or 9/5" Intensifier Systems—because they were specifically designed for medical diagnostic use.

The high degree of contrast detail perceptibility and image clarity produced by Norelco Intensifier Systems is partly due to precision optical engineering. High-speed, large-aperture lenses (f 1:0.75)—deemed impossible a few years ago—are exclusive features with Norelco Intensifier Systems.

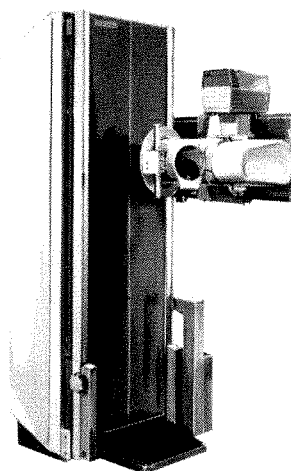
Two-channel distributors provide simultaneous viewing and recording: viewing via wide angle biocular mirror viewer or television, with cine or 70mm spotfilm recording. With the TV chain, video recorder and additional monitors for closed circuit TV are potential extensions of the system.

All Norelco Systems and components are completely integrated in design and manufacture. Norelco tables provide unusual operational facility with these systems—free from cumbersome ceiling suspensions.



DIAGNOST 70
with 9/5"
Image Intensifier

THE 9/5" IMAGE INTENSIFIER SYSTEM visualizes the 9" and 5" fields in a single intensifier tube. The 9/5" gives "panoramic" viewing of the 9" field, with immediate switch-over to the high resolution 5" center field, enlarged (1.8X) to the full diameter of the viewing screen.



DIAGNOST 50/6
with 6"
Image Intensifier

THE 6" IMAGE INTENSIFIER SYSTEM is clinically useful in such diverse applications as gastrointestinal examinations, heart catheterization, and fluoroscopic guidance in surgery. The compactness of the 6" Intensifier System is especially valuable for clinical investigation.

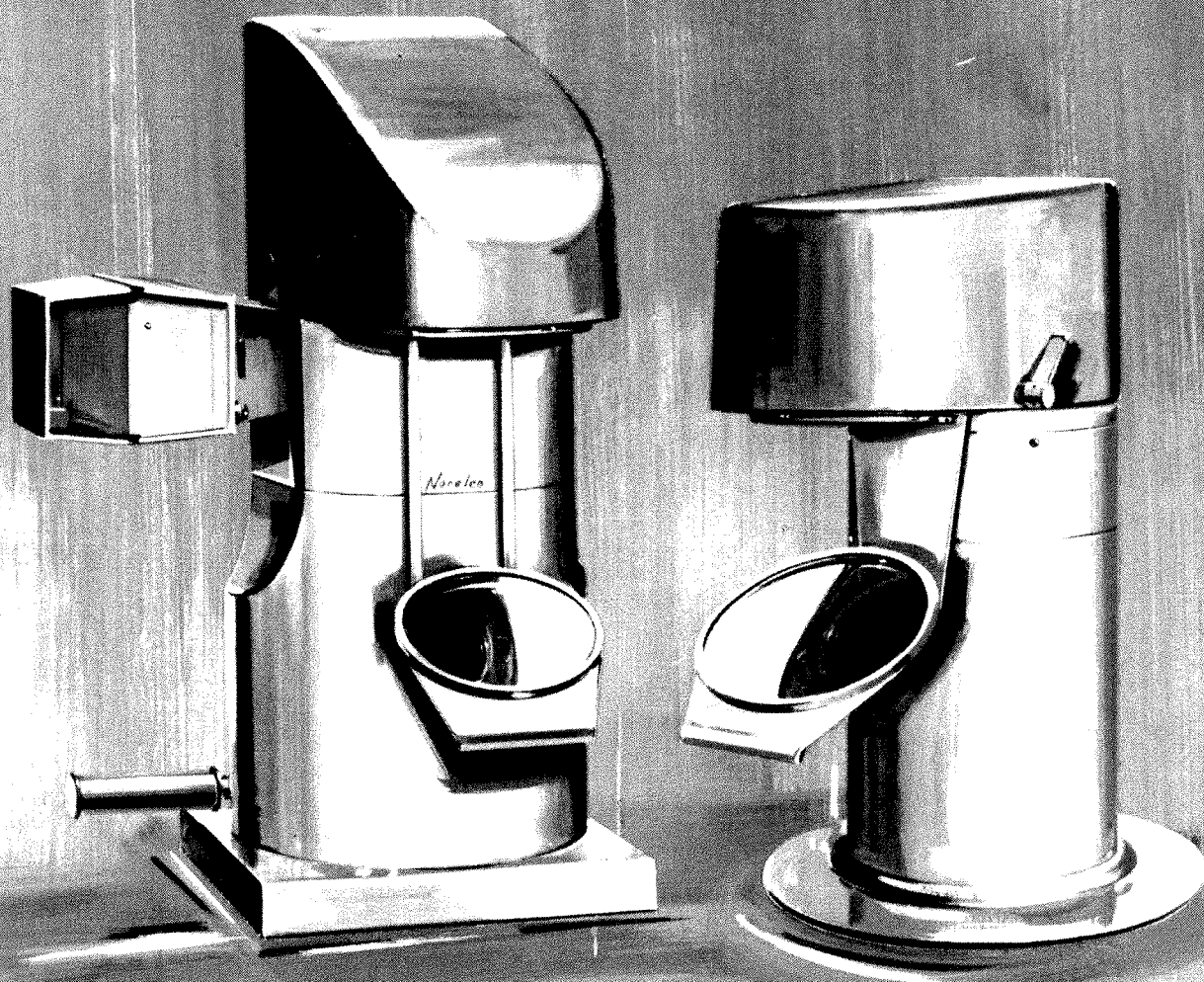
We are extremely proud of this technical achievement and would like to tell you about it in detail.

M 70



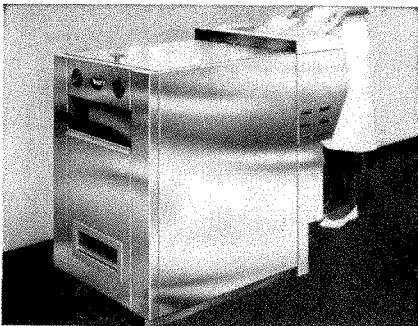
NORTH AMERICAN PHILIPS COMPANY, INC.
Professional Products Division, 100 East 42nd St., New York, N.Y. 10017

Image Intensifier Systems



	9/5"	5" (12cm)	6" (15cm)
Input Screen Diameter	9" (23cm)	5" (12cm)	6" (15cm)
Output Screen Diameter	13/16" (20mm)	13/16" (20mm)	9/16" (14.5mm)
Resolution (Central)	40 LP/inch	60 LP/inch	50 LP/inch
Resolution (Peripheral)	25 LP/inch	60 LP/inch	30 LP/inch
Intensification Factor (Average Gain)	5000	1500	5000
Conversion Factor*	36	12	36
Minimum Contrast	4%	4%	4%
Anode Voltage	25 kV	25 kV	25 kV
Viewing/Recording	Biocular Mirror Viewer. High Speed Lens f1:0.75. Transistorized Medical TV Systems—Plumbicon†/Vidicon. Cine 16/35mm pulsed or non-pulsed. Spot-film Cameras 70mm Single Frame/High Speed.		

*Per ICRU recommendations in National Bureau of Standards Handbook. †Plumbicon is a registered trademark.



Newest and smallest is the Pakorol-XF. Here is the processor/dryer that satisfies installations from the small office on up. Process film from 4" x 4" thru 17" x 36", up to 85 mixed sizes per hour. The cost is low and the quality results are high.

From the Pakorol line select the model that fits your requirements for:

- **CAPACITY**—to satisfy your needs
- **SPACE**—only a few square feet
- **WORK FLOW**—left or right hand
- **BUDGET**—minimum investment
- **MATERIALS**—process sheet or roll in screen film brand of your choice
- **CHEMISTRY**—of your choice
- **LOADING**—automatic or manual

Choose the PROCESSOR that gives you the choice...PAKOROL®

Any Pakorol processor model gives you an efficient and complete system for film processing and drying—hangerless—with proven, roller transport operation.

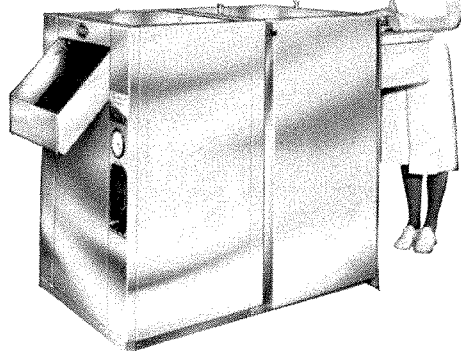
Pakorol processors are versatile. They will process and dry medical brand name screen film in the chemistry of your choice. Uniform processing and controlled drying are built-in. There is a Pakorol to fit the requirements and budget of a private office or clinic to the large medical center/hospital.

Want to be equipped for the new high-speed films? Modifications for 90-second and 3½ to 4-minute processing will be available this year for converting your Pakorol-X, XM and XF. Ask your Pako Distributor or write to Pako for full details.

PAKO

PAKO CORPORATION

6300 Olson Memorial Highway
Minneapolis, Minnesota 55440
PAKO FOR PROGRESS



The Pakorol-XM, giving a little more output, is ideal for offices or departments of all sizes. Many institutions find the "XM" works well for dual installation or for single use in several separate departments. Processes film to 17" width. The Pakorol-XM offers a unique combination of speed, small size, capacity and economy.



The Pakorol-X though big in capacity is still relatively small. Process 120—14" x 17" films per hour. Average 6½ minutes dry to dry processing.

ALL MODELS are of attractive polished stainless steel; no chains, all worm gear and roller operation.

AUTOMATIC SHEET FILM LOADER is available for the Pakorol-XF. Other accessories available. Pakorols are backed by Pako parts and trained service men at your area distributor. User training programs are frequently held at the Pako plant. Call your Pako Distributor now, or write to Pako.

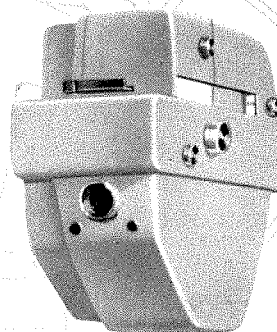
Newly-Designed Camera for G-E FLUORICON...

Switch from Cine to 70-MM spot filming in seconds!

**Compact new camera fully
programmed for
rapid sequence operation**

Many radiologists believe that 70-mm is the most satisfactory film size for spot filming. General Electric now meets this demand with two new models—13-in. and 10-in. focal length—of a 70-mm camera designed to accommodate all present Fluoricon image tubes. Photo-timing type control circuits are fully programmed and easily operated with a convenient foot switch. Camera reduces patient radiation dose significantly.

Investigate soon. Call your G-E x-ray representative or write X-Ray Department, General Electric Co., Milwaukee, Wisconsin 53201. Room A-81.



FEATURES

- Motorized Film Advance
- Single-Frame Or Sequence Operation
- Sequence Rate Up To Two Frames Per Second
- Well-Corrected, Folded Optical System
- Accepts 100-Ft. Film Supply (435 Frames)
- Individual 50-Frame Take-Up Cassettes
- Automatic Exposure Control
- Visible And Audible Film Supply Signals

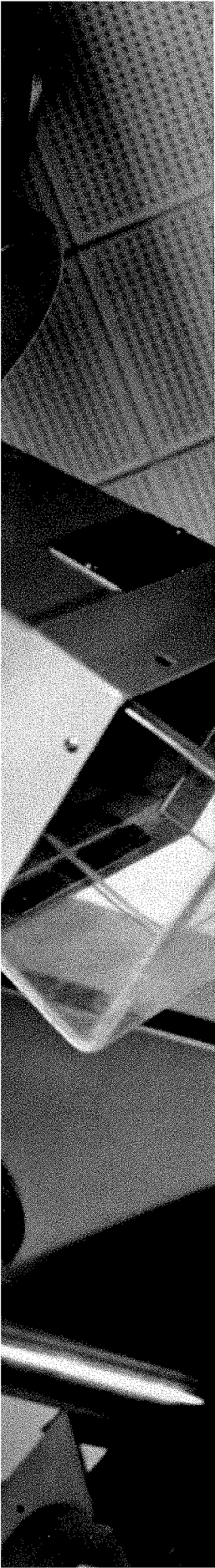
Progress Is Our Most Important Product

GENERAL  ELECTRIC

**Now! Dry, ready-to-read
radiographs in only
90 seconds with the new
KODAK Rapid Processing
X-OMAT® System.**

90 SECONDS
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The image consists of a single column of 21 identical white rectangular cards stacked vertically. Each card features the words "90 SECONDS" printed in a clean, white, uppercase, sans-serif typeface. The cards are positioned such that they overlap slightly, creating a sense of depth and repetition. The entire composition is set against a solid black background.



Westinghouse planned equipment protection keeps your X-Ray Department in continuous operation.

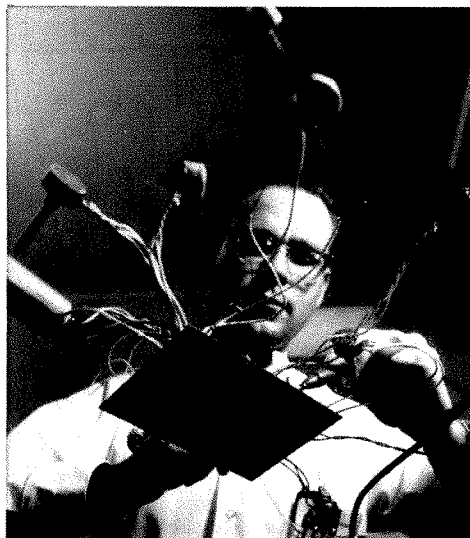
Westinghouse Sentinal Service™ is a complete X-Ray equipment care service. It's designed to keep your Radiology Department operating without costly interruptions—and tailored to your budget.

With one moderate, budgeted business expense you protect the life and reliability of your equipment. You head off the critical problems of case load back-up. And you rid yourself of the responsibility for equipment maintenance.

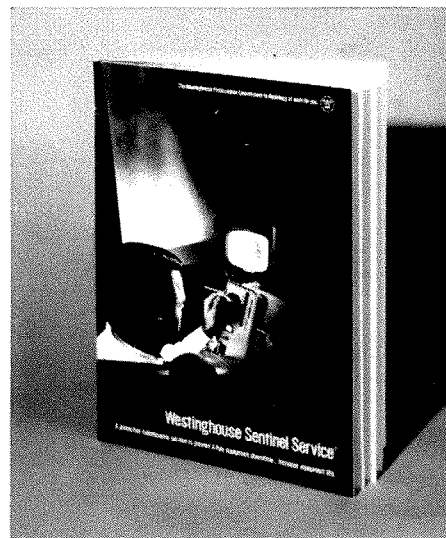
Westinghouse Sentinal Service gives you a planned protection program that features regularly scheduled equipment inspection and care.

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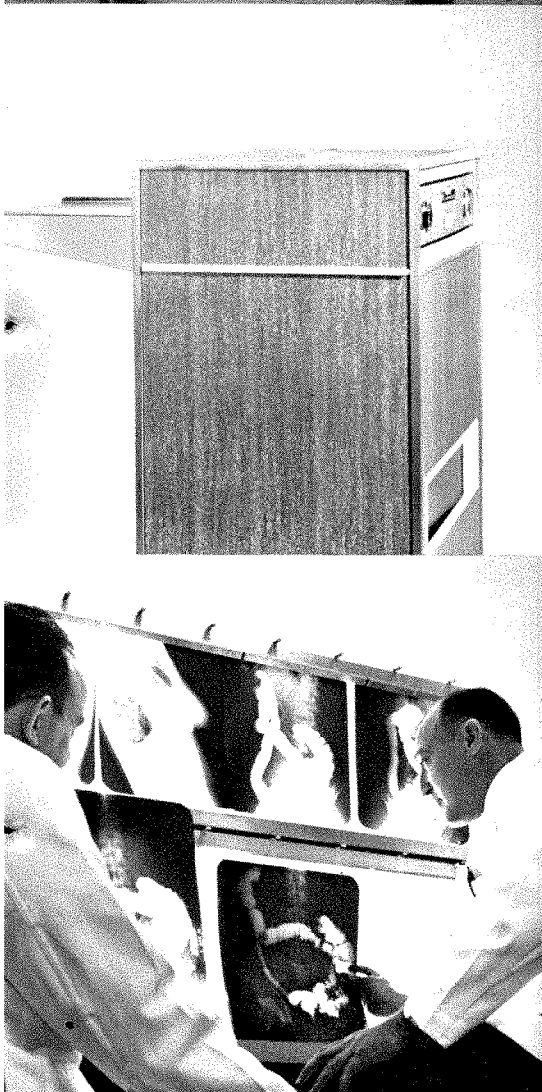
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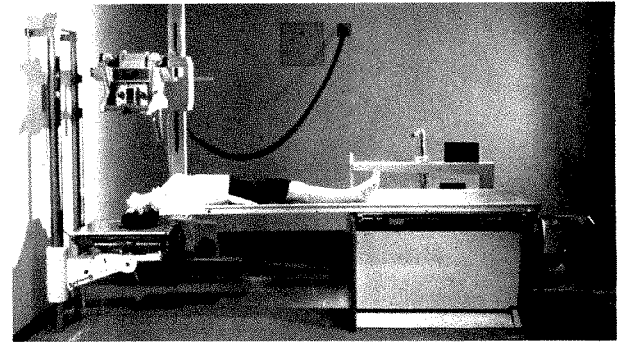
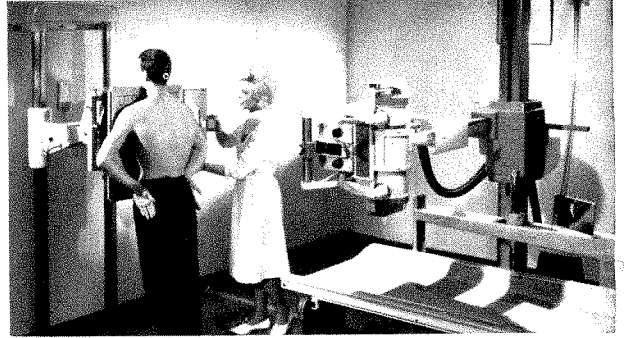
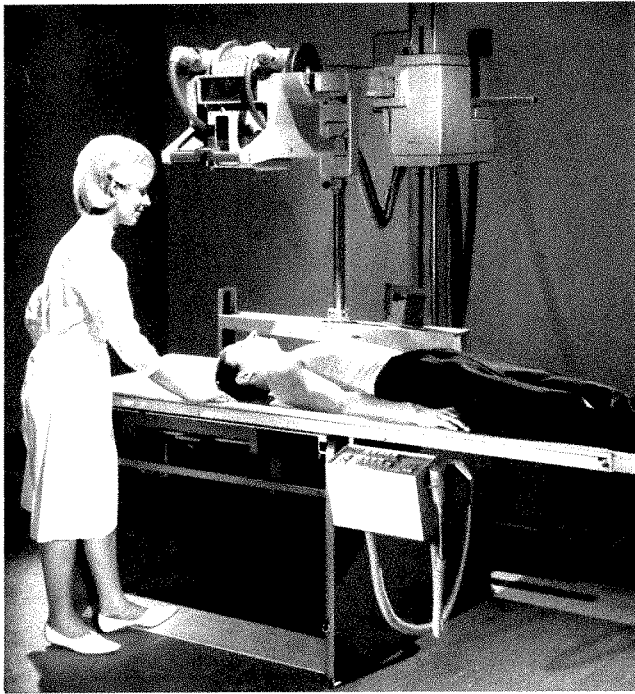
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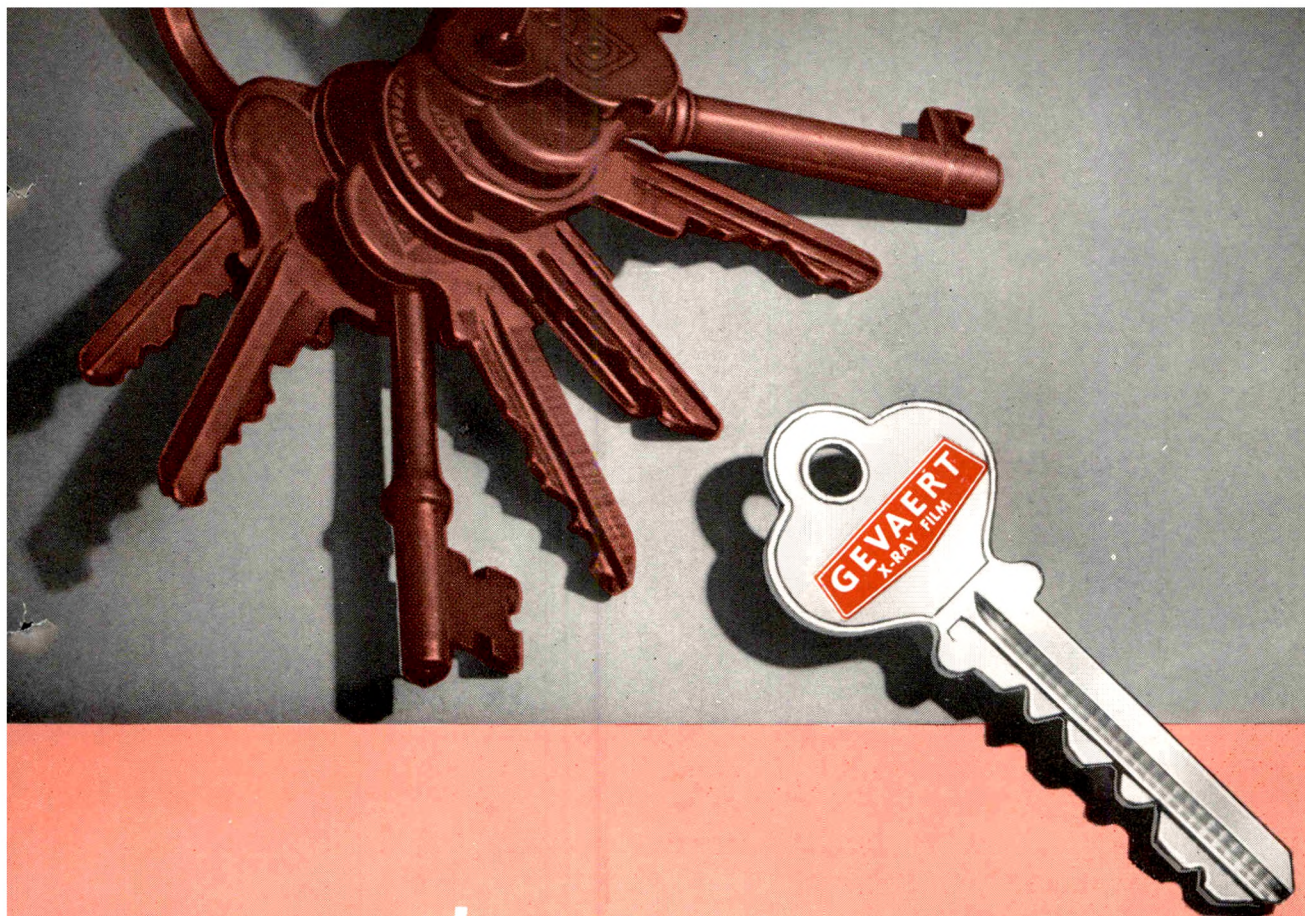


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Baker and Hodgson¹ of the Mayo Clinic and Mayo Foundation, reporting on a series of 1,207 cholecystographic examinations with TELEPAQUE in which all diagnoses were subjected to surgical and pathological verification, found 98 per cent of all the diagnoses were correct. All the nonvisualized gallbladders were found to be diseased, and the "increased accuracy of this diagnosis seemed to have a direct relationship to the medium employed". (The authors emphasize, however, the primacy of correct technical procedure and vigilance by the radiologist over the particular contrast medium used.)

Alderson² found TELEPAQUE 99 per cent accurate in cholecystography of 315 patients. He concluded that "TELEPAQUE is held to be the most satisfactory for routine radiological investigation of gallbladder symptoms". Six other groups of investigators have published similar results with TELEPAQUE which varied in accuracy from 95 to 100 per cent.³⁻⁸

only with Telepaque is such diagnostic accuracy so substantially documented

References: 1. Baker, H. L., Jr., and Hodgson, J. R. (Mayo Clinic and Mayo Foundation): Further studies on the accuracy of oral cholecystography, *Radiology* 74:239, Feb., 1960. 2. Alderson, D. A. (King's College Hosp., London): The reliability of Telepaque cholecystography, *Brit. J. Surg.* 47:655, May, 1960. 3. Rogers, J. V., Jr., Bonmati, J., Leigh, T. F., and Gay, B. B., Jr. (Emory University Hospital, Atlanta): Correlation of radiographic and surgical findings in gallbladder disease, *J.M.A. Georgia* 42:489, Nov., 1953. 4. Tillinghast, A. J. (New York): X-ray diagnosis in disorders of the biliary tract, *Rev. Gastroenterol.* 20:750, Oct., 1953. 5. Mauthe, H. (St. Agnes Hosp., Fond du Lac, Wis.): The accuracy of X-ray examination of the gallbladder, *Wisconsin M.J.* 53:473, Sept., 1954. 6. Garland, L. H. (San Francisco): New techniques in cholecystography, *Minnesota Med.* 39:433, July, 1956. 7. Whitehouse, W. M. (University Hospital, Ann Arbor, Mich.): Correlation of surgical pathology with Telepaque cholecystography in doses of two grams, *Surg., Gynec. & Obst.* 100:211, Feb. 1955. 8. Dietz, M. W., and Litton, L. D. (Springfield, Mo.): Syllabus of cholecystography, *GP* 14:109, Oct., 1956. *Dosage:* The TELEPAQUE tablets (0.5 Gm. each) are preferably administered from 10 to 12 hours before the time

scheduled for cholecystography. At about 10 P.M., 6 tablets should be swallowed, each with one or two mouthfuls of water (with a total of a full glass of water). In patients where visualization of the extrahepatic ducts is especially indicated, from 10 to 12 tablets have been recommended. In patients with thin or normal build, weighing less than 150 pounds, 4 tablets may prove sufficient.

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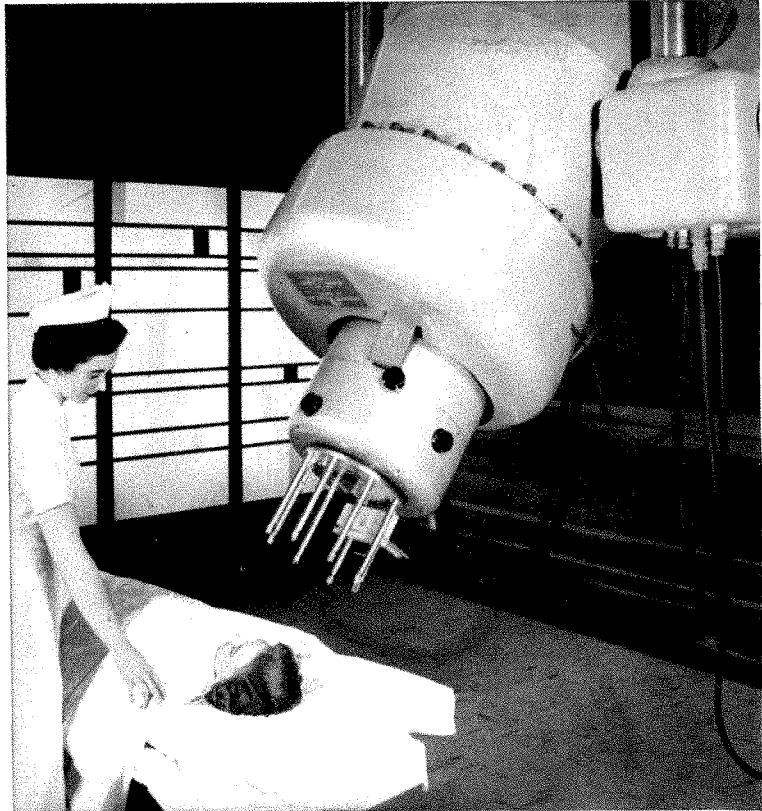
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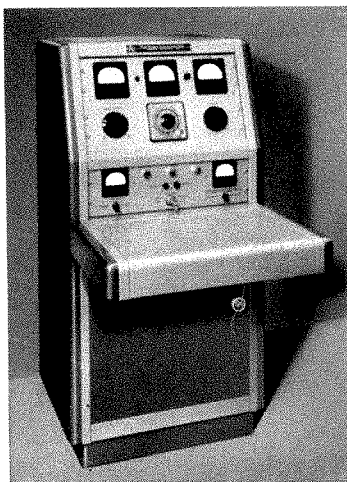
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RADIOISOTOPE SCANNING WITH A SYSTEM FOR TOTAL INFORMATION STORAGE AND CONTROLLED RETRIEVAL*

By ABBAS M. REJALI, M.D., HYMER L. FRIEDEL, M.D., and EARLE C. GREGG, Ph.D.

TO MAKE radioisotope scanning techniques effective and valuable, small differences in the distribution of the radioisotope and, therefore, small differences in the intensity of the detected signal must be identified and the statistical significance of these small differences must be readily determinable.

In order to observe small differences, it is essential to accentuate them, otherwise the eye will often fail to recognize them.

To accentuate or sharpen these small differences many methods have been proposed. Most important among these are:

1. The introduction of pre-selected count rate cut-off or erase levels.^{2,6} This eliminates any signal below a predetermined level, thus marking sharply the difference between counts above the cut-off level and counts below the cut-off level. The disadvantage of this is obvious, since it irretrievably throws away information which might prove to be valuable.

2. Contrast enhancement utilizing appropriate film characteristics in photo-

scanning.⁵ The difficulty here again is that the contrast enhancement is generally uncontrolled and the original data irretrievably altered.

3. Color coding⁴ for various radiation levels. Differences in intensity may be identified by differences in colors. The use of color limits the number of counting rate levels which one may identify. For low counting rate levels, the number of colors which is available (usually varying from 6 to 10) may be sufficient for determining significant differences. For high counting rates, there are insufficient compartments (colors) to identify all the significantly different levels.

All of these proposals, as we have indicated, have important defects in that they require prior selection of critical factors or involve permanent distortion of the original information. This is of serious consequence in a system where information is already very scarce and must be carefully handled.

We have, therefore, developed a system in which there is permanent storage of all

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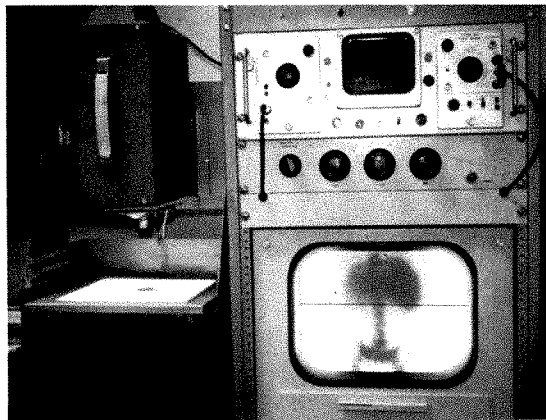


FIG. 1. Data extraction and presentation system which consists of special videcon television as well as a system for presenting an accurate "profile" of any selected "slice" on an oscilloscope.

of the available information without prior modification of any kind or pre-selection at any level.³

The information is stored on special film and may then be readily subjected to detailed study by utilizing a large number of erase levels and large number of known controlled contrast adjustments. These erase levels and contrast enhancements can be applied quickly so that numerous adjustments can be viewed in a few seconds.

Since the stored information is never permanently modified, it is always possible to return to the original data if the contrast and erase adjustments are unsatisfactory for any reason.

The new scanning system that we shall briefly outline and which became operational in 1963 consists of a commercially available frame and two opposing over and under scintillation detectors with choice of opposing versus single collimators.

Programming is performed through a control panel which permits selection of scan area up to 2 feet $\times$ 6 feet and scan speeds from 3.5 inches/min. to 46.7 inches/min. and line spacing from 1/16 to 13/16 inches.

In the recording system, signals from the detectors, following amplification, are passed through a pulse height analyzer to produce a spot on the oscilloscope. The position of the spot on the face of oscillo-

scope is determined by the position of the detectors. This spot can be adjusted to project aperture size or smaller, but this is not critical since the counting rate will generally produce overlay and density addition on the film. Later, dots can be blended on the data presentation system by defocusing.

A counting rate meter is provided for continuous monitoring and adjustment of the pulse height discriminator, but since it is not in the recording circuit, diminished resolution by memory effect secondary to the rate meter lag is eliminated.

No modification of the pulse rate is made since no scaling devices are used in the circuit and all information is recorded without modification.

All information is recorded on a polaroid camera (a "dot on film" procedure¹) with a transparent negative for data presentation and analysis.

To view the information stored in the film and for presentation and analysis a videcon television replay system (Fig. 1) is utilized.

This system uses special low level cut-off (background erase) and nonlinear gain (contrast enhancement) as well as presenting an accurate "profile" of the counting rate at any selected position "slice" on an oscilloscope. A line blanking circuit produces a black line on the kinescope picture that defines the position of the "slice" for assessment of the distribution of the isotope in the organ as well as volume uptake of various organs in the same scan. A simple rotation of the film (Fig. 3, *A-F*) allows a profile to be made in any desired direction.

The resolution of the picture can be changed by an adjustable bandwidth, and a polaroid camera is used to take pictures of the scans appearing on the kinescope. There is no dependence on a counting rate meter which may produce lag and loss of resolution.

CLINICAL RESULTS

The most important consideration in scanning instrumentation, obviously, is how well it represents differential deposits

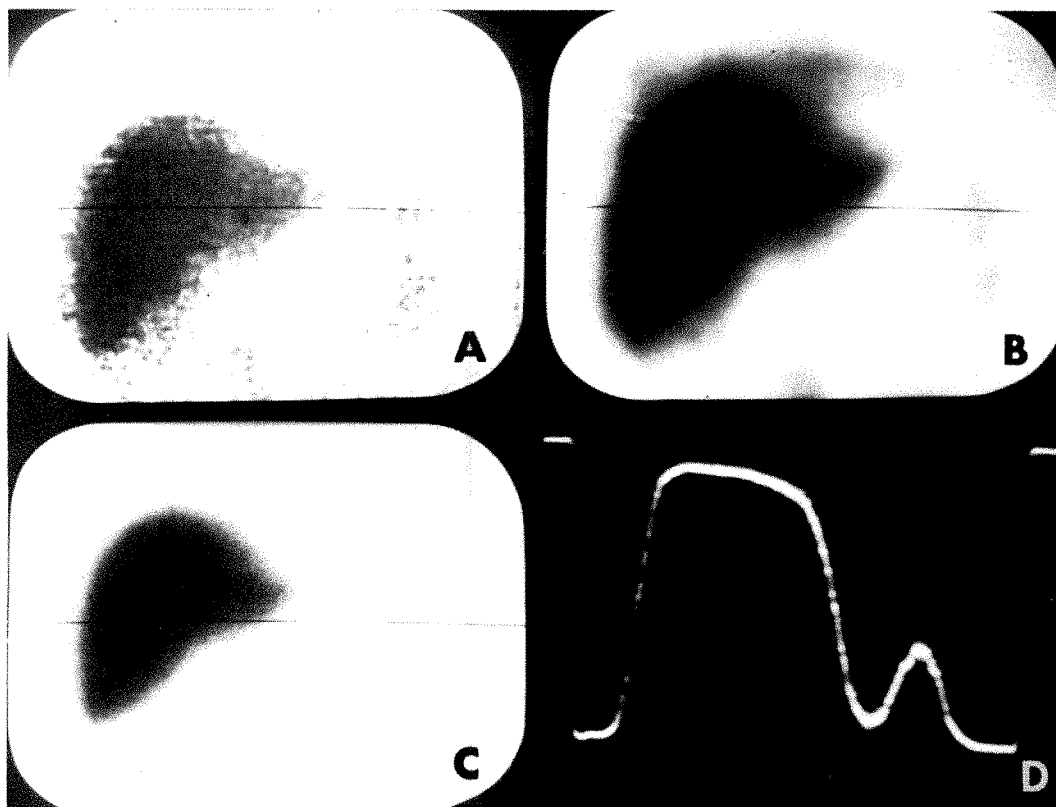


FIG. 2. Normal hepatoscans showing (A) stored information and (B and C) successive modifications, with the transverse "slice" through the liver on C. (D) Count rate profile is shown on oscilloscope.

of isotopes in the scanned area.

Figures 2 through 15 are typical normal and abnormal scans of different organs illustrating our total information method, data modification and analysis. Many degrees of background erase and contrast enhancement readily applied without alteration of the original data are presented. The application of profile analysis is also shown.

Figure 2, A-D is typical of a normal hepatoscan using 300 μ c of colloidal gold Au^{198} . The solid line crossing the liver and spleen represents "slice" through the organ

for assessment of distribution of radioisotope. The profile line can be moved throughout the scanned area. Figure 2D

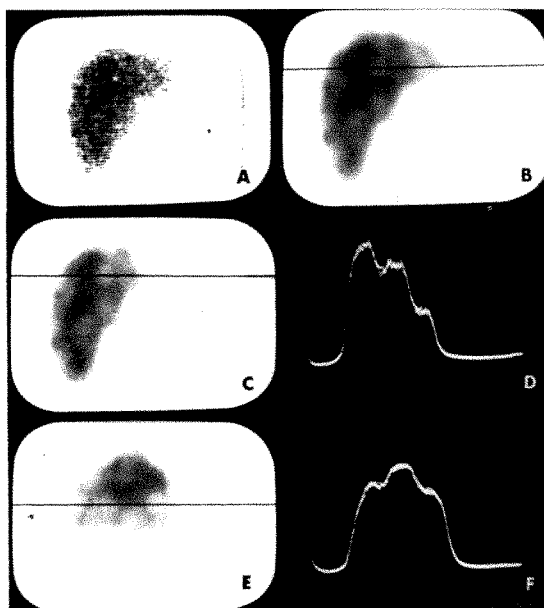


FIG. 3. (A, B, C and E) Hepatoscans with successive erase levels showing space occupying lesions. (D and F) Profiles showing a transverse "slice" through the liver in C as well as one passing between right and left lobe in E. The latter is accomplished by simply rotating the original film on the view box.



FIG. 4. (*A* and *B*) Modified hepatoscans demonstrating enlarged spleen and abnormal uptake of gold in spleen and bone marrow. Solid line in *B* passing through the liver, bone marrow and spleen represents profile line "slice." (*C*) Profile showing relative uptake of gold in the spleen, bone marrow and liver.

shows the profile of the "slice" on the oscilloscope and reveals uniform uptake of gold in the liver and slight uptake of gold in the spleen. Figure 2, *B* and *C* is a presentation with successive erase and contrast enhancement. In Figure 2*C* most of the thinner portion of the spleen and liver has been

eliminated, but the distribution of gold in the remaining portion of the liver still remains homogeneous.

Figure 3, *A-F* is typical of abnormal liver scans. This patient, a 5 year old female, had a left nephrectomy for a Wilms' tumor at the age of 4 years. A recent chest roentgenogram revealed the presence of a solitary nodule in the left lung, and a lobec-

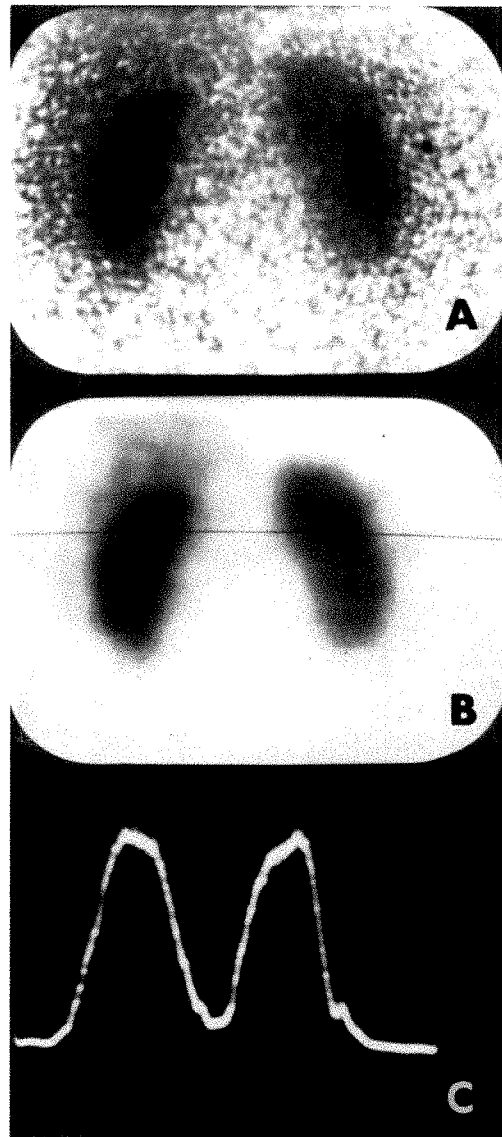


FIG. 5. (*A*) Stored information without modification. (*B*) Following partial erase. The profile line passes through both kidneys. (*C*) Profile on oscilloscope showing equal uptake of chlormerodrin in both kidneys.

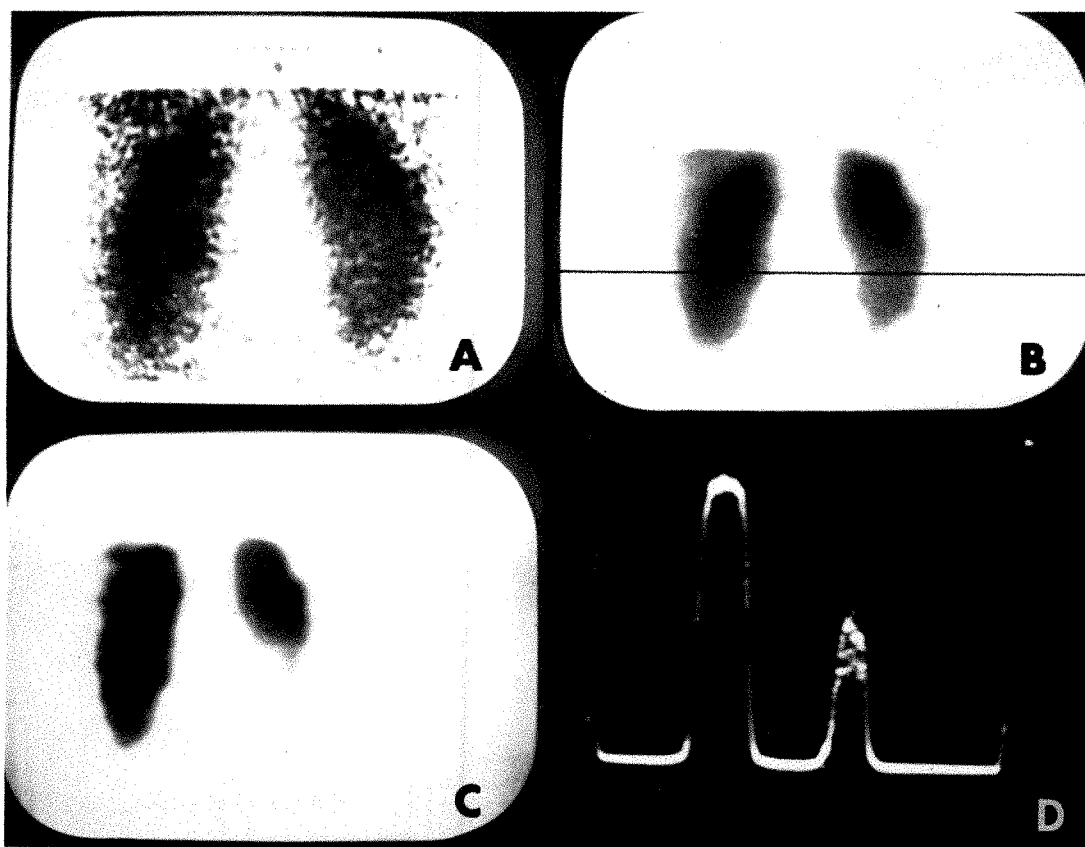


FIG. 6. (A) Total information renal scan not demonstrating any abnormalities. (B and C) Following proper erase and contrast adjustment, scans reveal decreased uptake in the lower half of left kidney. (D) Profile showing relatively lesser uptake of chlormerodrin in the lower half of left kidney.

tomy was considered. To rule out metastases elsewhere, a liver scan was requested. Figure 3A shows the original information without erase or contrast enhancement. The liver appears to be slightly enlarged for the age and weight of this child, but definite evidence of a space occupying lesion is not easily identifiable. The effect of successive erase and contrast adjustment is seen in Figure 3, B, C and E, showing multiple areas of decreased uptake representing space occupying lesions not visible in the scan without erase and contrast modification. The "profile" from the oscilloscope shows areas of decreased activity corresponding in location with the areas of space occupying lesions.

A typical hepatoscan of advanced cirrhosis is seen in Figure 4. The patient had the usual history consistent with cirrhosis.

The hepatoscan (Fig. 4A), made with colloidal gold Au^{198} , reveals enlargement of the liver and spleen. The uptake of gold in the spleen and bone marrow appears to be abnormally high as a result of depressed liver function and circulation. Figure 4B shows the profile line through the lower pole of the liver, spleen and 3rd lumbar vertebra, assessing relative activity in these areas, and Figure 4C, the profile obtained. The lower pole of the liver shows less activity than the lower pole of the spleen.

Figure 5A is a normal renal scan performed with $300 \mu\text{c}$ of Hg^{197} tagged chlormerodrin without erase and contrast enhancement. Figure 5B is the same scan showing the profile line through both kidneys following erase and control adjustment. The uptake of chlormerodrin appears to be uniform in both kidneys. The

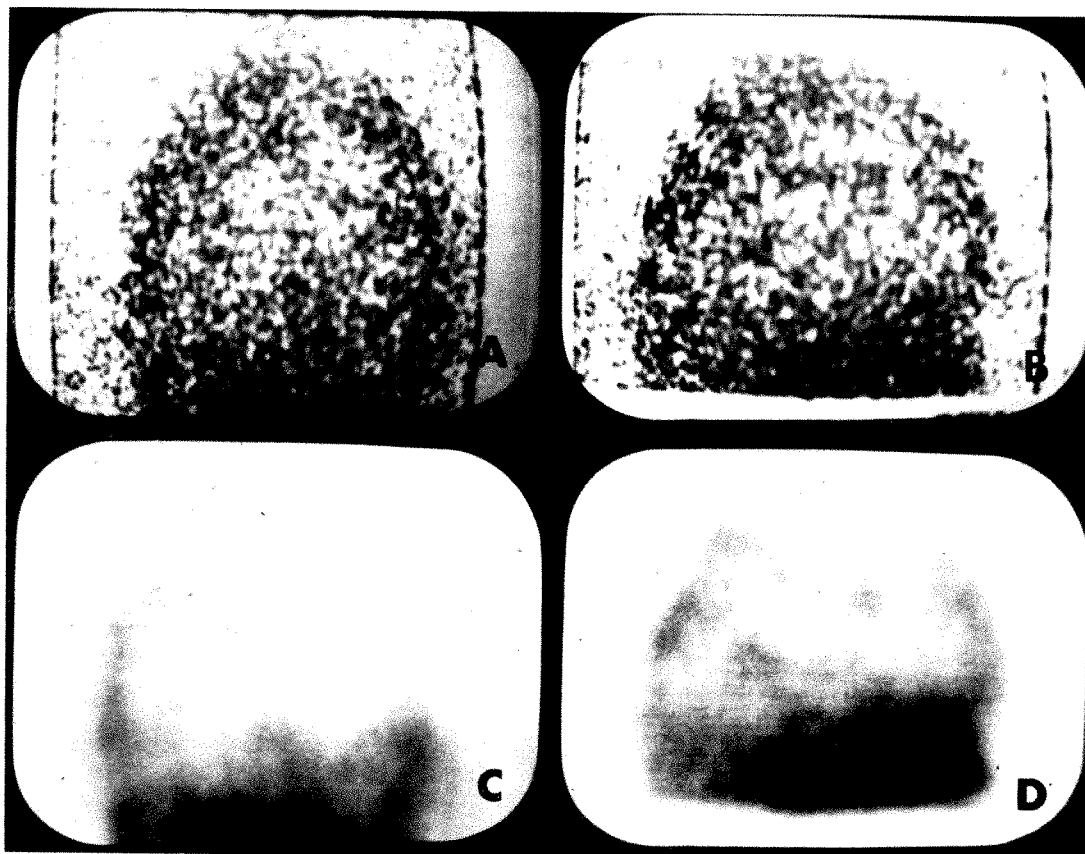


FIG. 7. (*A* and *B*) Normal cephaloscans in posteroanterior and lateral view without modification. (*C* and *D*) Normal cephaloscans following adjustment of contrast and erase levels.

tracing of the profile "slice" is very valuable in evaluation of the distribution of chlormerodrin in each kidney as well as the relative volume uptake in both kidneys. The profile (Fig. 5C) reveals equal activity over both kidneys.

A renal scan of a 44 year old male is shown in Figure 6A. A nephrotomogram and retrograde pyelogram showed no definite abnormalities. The stored data without erase and contrast adjustment (Fig. 6A), like many conventional systems not possessing the capability of storing the original information and eventually permitting appropriate modification, showed no definite abnormality. The same scan following proper erase and contrast adjustment (Fig. 6B) reveals a normal right kidney, but the lower half of the left kidney showed definitely decreased uptake which was far better visualized following further erase

and contrast adjustment (Fig. 6C). The profile in Figure 6D shows the marked decrease in the uptake of chlormerodrin. This proved to be an adenocarcinoma on laparotomy.

For cephaloscans with this system we have used both Hg^{197} tagged chlormerodrin and $\text{Tc}^{99\text{m}}$. Figure 7, *A* and *B* represents a normal posteroanterior and lateral cephaloscan with chlormerodrin, without modification and Figure 7, *C* and *D* with erase and contrast adjustment. The usual landmarks, such as facial and temporal muscles, are well visualized, but blood pools, such as vascular sinuses, are sharply diminished since we scan adults 5 to 6 hours following administration of the agent when the blood level of chlormerodrin is relatively low.

Figure 8 is one of our typical abnormal cephaloscans. This patient was admitted to the hospital because of a possible brain

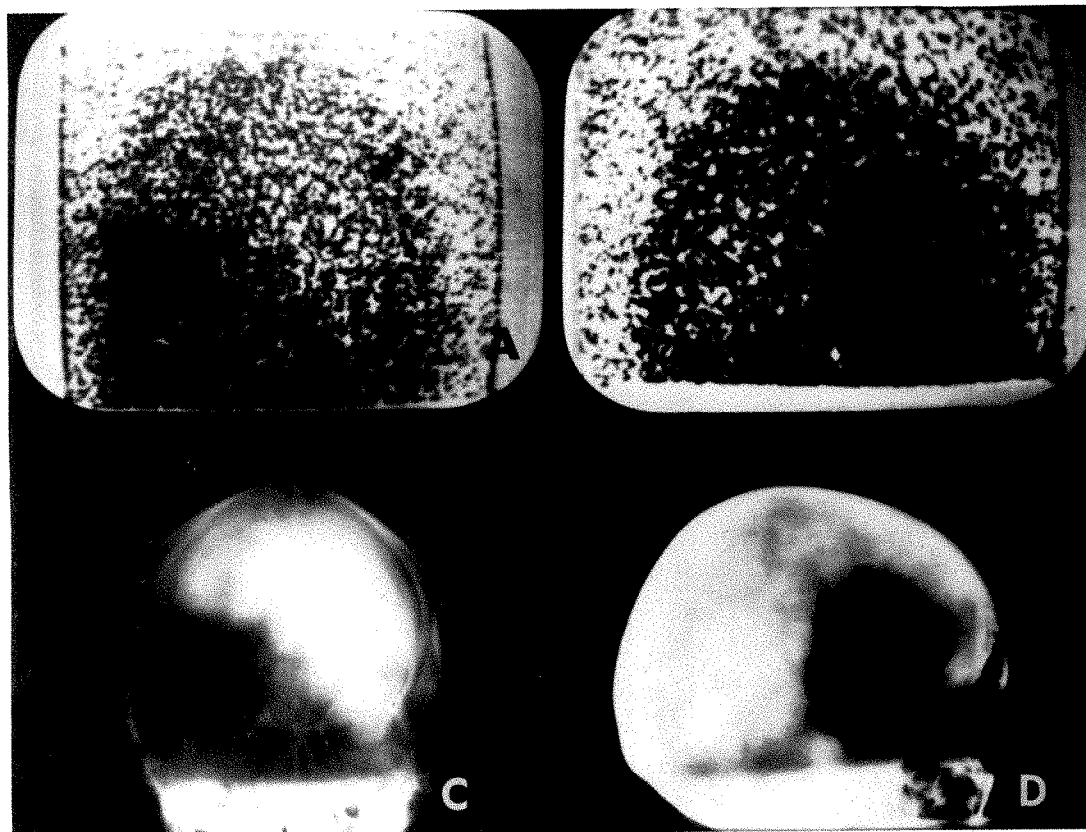


FIG. 8. (*A* and *B*) Abnormal cephaloscans in original posteroanterior and lateral views without modification. (*C* and *D*) Abnormal cephaloscans following erase, contrast enhancement and superimposition on skull roentgenograms.

tumor. Figure 8, *A* and *B* shows postero-anterior and lateral cephaloscans made with Hg^{197} tagged chlormerodrin without alterations. Definite extensive abnormal concentration of chlormerodrin is seen in the right fronto-temporo-parietal region, which is better visualized in Figure 8, *C* and *D* following erase and contrast adjustment. An accurate localization of the lesion is indispensable for satisfactory orientation of the clinician. This can easily be accomplished with our data presentation method by superimposing the scan on the skull roentgenogram (Fig. 8, *C* and *D*). At surgery, an astrocytoma, extending from the right frontal lobe to the temporal and parietal region, was found.

This method has been applied to lung scanning. I^{131} tagged macroaggregated human serum albumin (MAA) was used. The uptake of MAA in both lungs is uniform

when there is no disturbance of pulmonary blood supply and when there is no pathology displacing the pulmonary capillaries (for example, emphysematous blebs). A typical normal lung scan is seen in Figure 9*A*. To obtain more quantitative data than those provided by the pulmonary scan and to evaluate the uptake of MAA in each lung and relative uptake in both lungs, our profile system may be applied. The profile line is seen crossing both lungs in Figure 9*A*, assessing the distribution of MAA at the site. The profile is shown in Figure 9*B* and reveals equal uptake of macroaggregated human serum albumin in both lungs.

Figure 10 is a lung scan of a 44 year old patient who was admitted to the hospital with a history suggesting cardiac disease of long duration. Since the lung scan shows the relative uptake of MAA in both lungs which in turn indirectly evaluates the blood

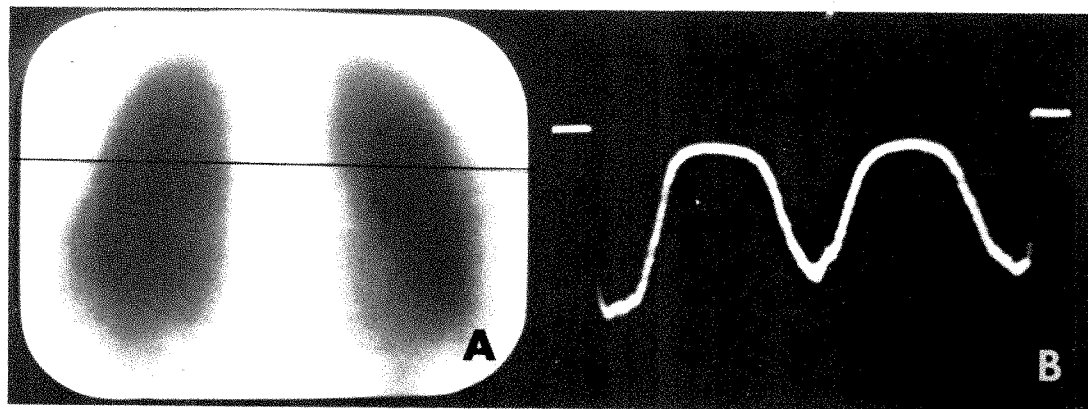


FIG. 9. (A) Normal lung scan and (B) profile through the mid-lung fields.

supply to the lungs from the right ventricle, an attempt was made to see whether any alteration in right heart flow to the lungs could be visualized. The uptake of MAA is uniform in the right lung (Fig. 10A) but an

essentially complete absence of deposited MAA with exception of a minimal amount of uptake in the upper part of the left lung is seen. The "profile" of both lungs (Fig. 10B) shows the relative uptake. Since there

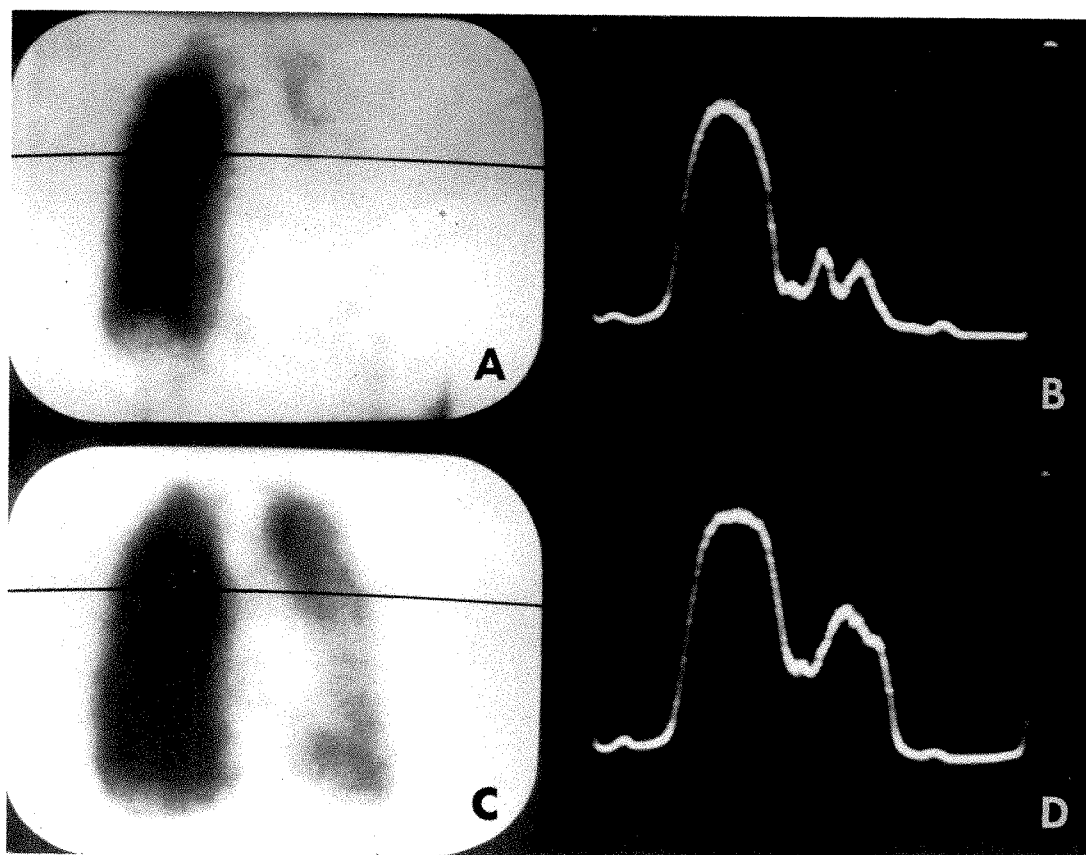


FIG. 10. (A) Lung scan and (B) profile showing uniform uptake of MAA in the right lung and minimal uptake in the apical and subapical region of left lung as a result of patent ductus arteriosus. (C) Lung scan and (D) profile following resection of patent ductus.

was no clinical evidence of pulmonary infarct but a long history of murmur, it was thought that this could be a result of shunting of blood from the aorta into the left pulmonary artery. Partial obstruction of the left pulmonary artery could not be excluded. Cineangiocardiology and later thoracotomy revealed a patent ductus arteriosus and marked shunting of the aortic blood into the left pulmonary artery. The patent ductus was resected and a lung scan (Fig. 10C) 2 months later revealed higher uptake of MAA in the left lung than before, but the blood supply to the left lung still appeared to be less than that on the right.

Figure 11 demonstrates the method as applied to bone scanning. In this case Sr^{85} was utilized. The patient had a carcinoma of the breast with known metastases. In

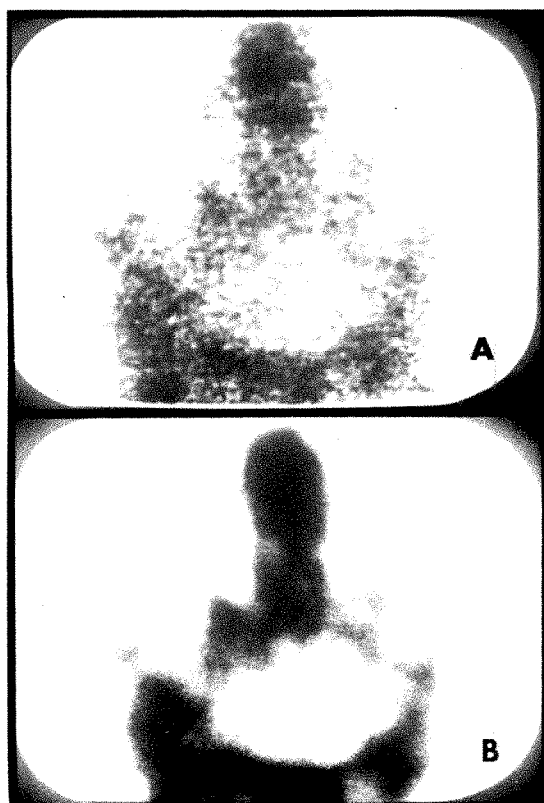


FIG. 11. (A and B) Pelvis and lower lumbar spine showing extensive abnormal uptake of Sr^{85} . (A) Stored information without modification. (B) Following adjustment of erase and contrast.

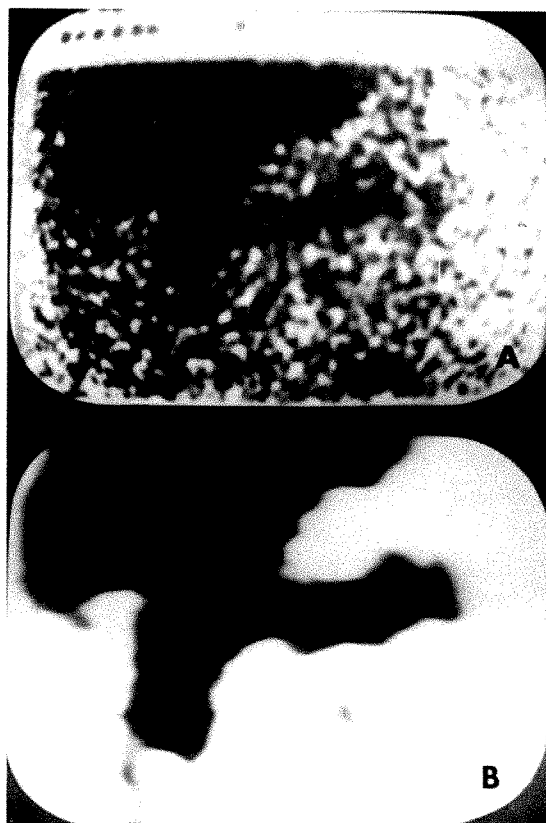


FIG. 12. Normal pancreatic scans showing (A) unmodified total information and (B) following erase and contrast enhancement.

Figure 11A, the data are shown without modification and areas of abnormal uptake are not well visualized or delineated. Following proper adjustment (Fig. 11B), extensive abnormal uptake is seen.

Visualization of the pancreas represents a special problem. Although the uptake of selenium tagged methionine, the material of choice at present, is considerable in the pancreas, there are large amounts of radiomethionine deposited in surrounding and superimposed structures, such as the liver, kidneys, stomach and bowel. This results in a relatively modest differential which is generally very difficult to identify. The method described in this paper is particularly effective in the visualization of modest or small differences. The prejudgment required in conventional scanning methods for visualization of the pan-

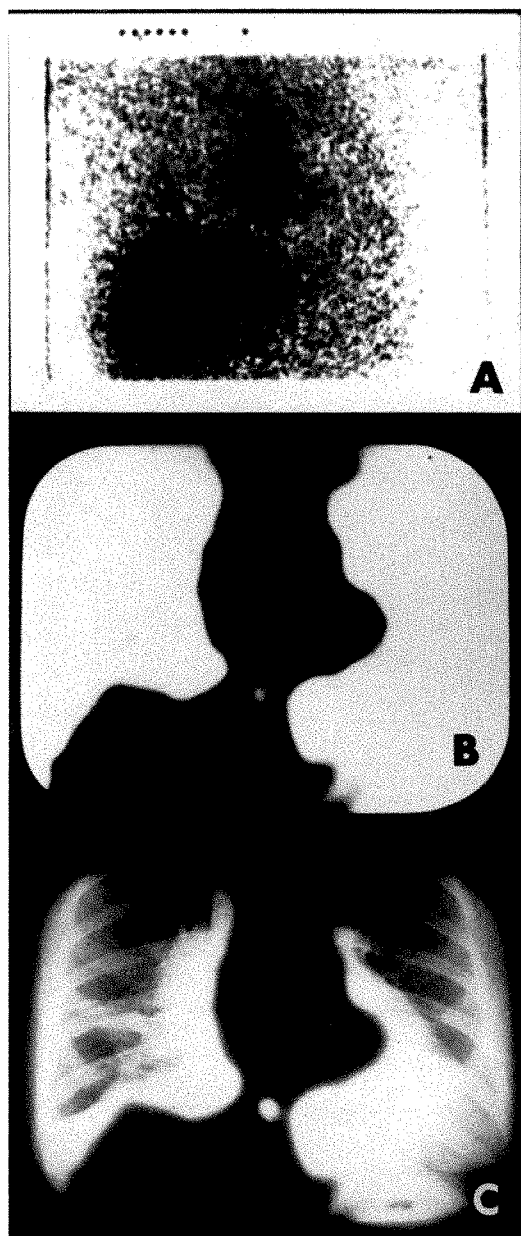


FIG. 13. Blood pool scans. (A) Total information without modification. (B) Following proper modification and (C) superimposition on chest roentgenogram.

creas in setting the appropriate background erase or contrast enhancement is especially critical under these circumstances and may result in failure. Figure 12 shows a typical normal pancreatic scan made with Se^{75} tagged methionine. Figure 12A shows the

unmodified record. Figure 12B is the same scan following erase and contrast enhancement. The head, body and tail of pancreas are well visualized.

Figure 13 is an example of a blood pool scan. A previous chest roentgenogram of this patient with known Hodgkin's disease revealed right pleural effusion and enlargement of the cardiac silhouette. A cardiac blood pool scan (Fig. 13B) following proper erase and contrast adjustment reveals a marked discrepancy between the cardiac blood pool, which appears normal, and the markedly enlarged cardiac silhouette, strongly suggesting an enlarged pericardial sac (Fig. 13C).

Figure 14, A-D is typical of normal myocardial scans using Cs^{131} in the form of cesium acetate.⁷ The normal myocardium shows a large differential uptake of radioelements as compared to areas within it which have disturbed blood supply, such as recent or old myocardial infarcts. These differences are often partially obscured and minimized by the deposition of radioelements in the superimposed tissue, particularly pectoral muscles. Therefore, it becomes important to utilize a method which accentuates small differences and permits their identification. In the original unmodified information (Fig. 14A) distribution of Cs^{131} is seen throughout the scan areas as expected. Presentation with erase and contrast adjustment (Fig. 14B) shows a high uptake of Cs^{131} in the myocardium, liver and pectoral muscles in the anterior chest wall, which incidently appear more prominent on the right side in a right-handed person. Muscles in the right upper arm which happen to be in the field of the scan are also shown. An area of decreased activity is seen in the midline between the medial aspect of myocardium and upper medial aspect of the liver which corresponds to the lower part of the sternum and is the result of absorption of radiation by this bone. Further erase and contrast adjustment (Fig. 14C) erase the thinner part of the pectoral muscles and muscles in the

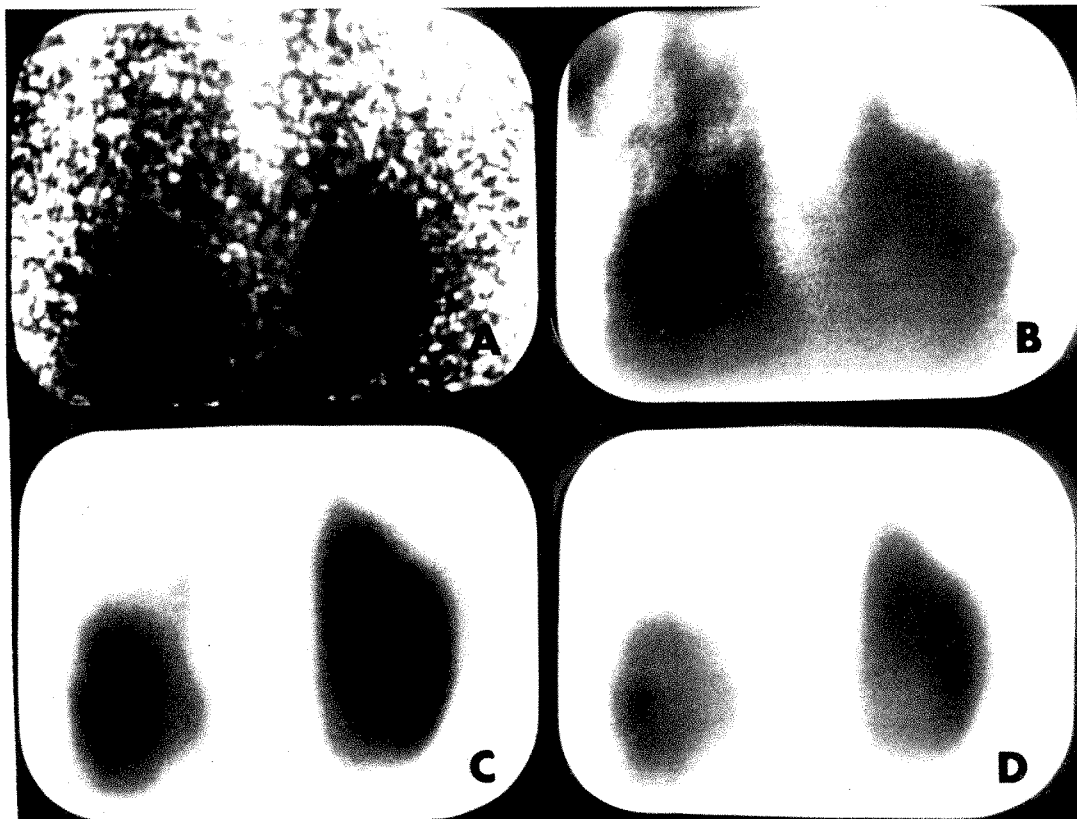


FIG. 14. (A-D) Normal myocardial scans showing original total stored information and successive adjustments of contrast and erase levels.

upper part of the right arm, as well as thinner parts of the liver and myocardium posterior to the sternum.

To avoid faulty diagnosis of a myocardial infarct, chest roentgenograms in each case are compared to the myocardial scan to rule out overlying ribs. This may cause areas of decreased uptake which might be confused with an infarct.

Figure 15A demonstrates the original stored data of a scan of a 29 year old male and Figure 15B, following proper adjustment of contrast and background erase, shows a large defect in the myocardium extending to the cardiac base and involving two-thirds of the lateral border. In Figure 15C the scan is rotated about 45°. The solid line passing through the heart and liver represents the profile line. Figure 15D indicates the relative uptake of Cs^{131} . The

patient had the typical history and findings of myocardial infarction. The electrocardiogram indicated a large inferior-anterior and lateral myocardial infarction. The extent, location and configuration of this lesion are well demonstrated on the scan.

DISCUSSION

Loss of information and failure in radioisotope scanning techniques are not infrequent with most systems because the final presentations involve pre-judgment as to the appropriate cut-off level, proper degree of contrast enhancement or both. If this, for any reason, proves unsatisfactory, the only recourse is repetition of the study which is time consuming and inconvenient to the patient and often requires additional administration of the radioisotope.

The significant aspect of the method

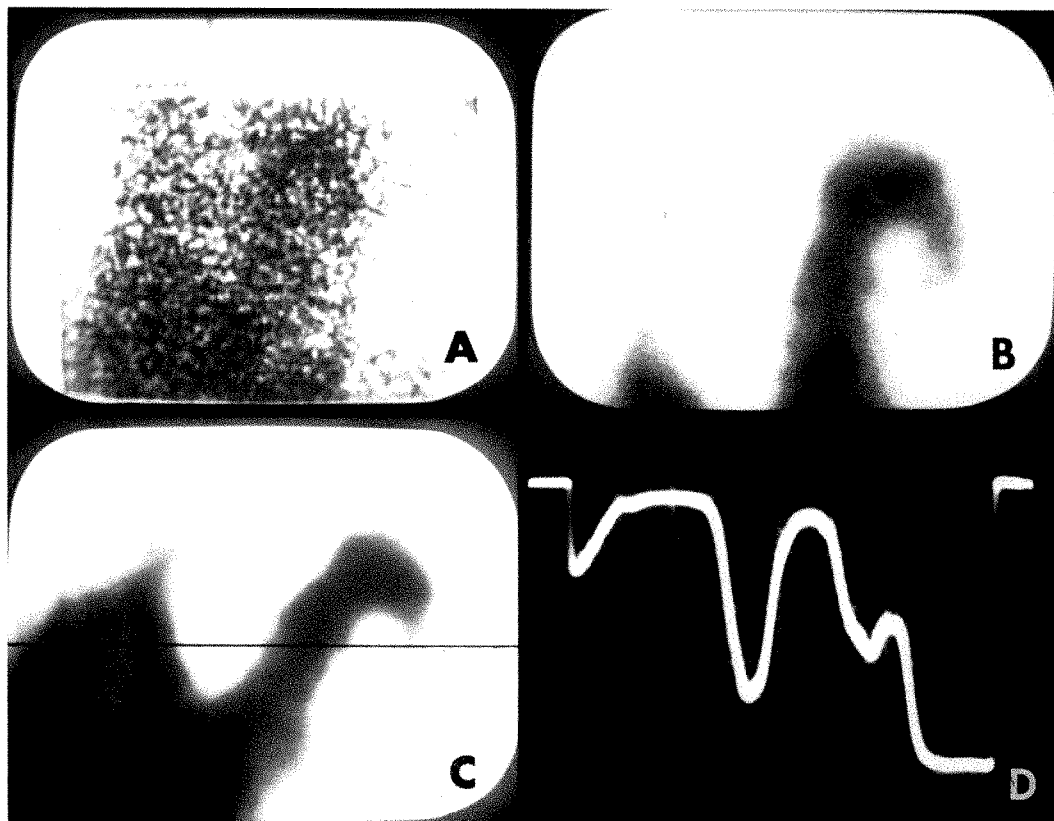


FIG. 15. (A) Myocardial scan without modification and (B and C) two adjustments of contrast and background erase level showing defect in the left lateral border extending to base. Profile line location shown in C. (D) Profile on oscilloscope.

described in this communication is that the storage and display of the information are independent. The stored data allow immediate or delayed recall and detailed examination with little or no loss of information. Innumerable erase levels and varying degrees of contrast enhancement can be readily applied to the stored data in a few seconds.

Profiles in our data presentation system also provide immediate plots of count-rate versus position for any selected one dimensional "slice." This latter feature allows the assessment of the distribution in the uptake of the organ under study as well as the relative uptake in the various organs in the scan area. Once these differences are established, it is possible to test them for statistical significances.

SUMMARY AND CONCLUSION

This presentation emphasizes the improved clinical results obtained from our present radioisotope scanner and data presentation system. The essence of the system is that all available information received by the detector is stored without prior modification in a permanent memory. A special vidicon television replay system under carefully controlled circumstances permits immediate and innumerable degrees of erase and contrast enhancement to be applied to the stored data in a few seconds. A profile representing the count rate through any slice in the scanned area may be performed to determine relative distribution.

At present, the method appears to be particularly valuable in identifying small

differences and presenting them in a clearly demonstrable fashion.

Abbas M. Rejali
Department of Radiology
Western Reserve University
Cleveland 6, Ohio

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VISUALIZATION OF THE LUNG BY METHODS OF SCINTIPHOTOGRAPHY*

By MERLE K. LOKEN, Ph.D., M.D.,† and ROBERT D. BUGBY, M.D.‡

MINNEAPOLIS, MINNESOTA

MUCH attention has been given in recent years to the visualization of disease in various body organs by methods of scintiphotography. The use of radioactive materials for obtaining scintiphotograms of the lung has been a relatively recent addition to these studies. The term "scintiphotogram" is used here to define the visual presentation of the nuclear instruments used. The best known of these instruments is the rectilinear scanner which has been used in the majority of our studies. The usual read-out for the scanner is the photo-scan. For the past 10 months, we have had a scintillation camera in our clinic. This device has an 11 inch diameter crystal backed by 19 phototubes, each of which sees scintillations occurring in the crystal. The electrical impulses from these photomultiplier tubes are fed through an analyzer which is capable of determining the site of the scintillation event and biases a cathode ray tube to display this as a single flash on the cathode ray screen in the same geometric relationship as the initial event. This is then photographed with a Polaroid camera.

Early attempts to visualize the lungs involved the use of radioactive ceramic microspheres impregnated with radioactive materials.¹¹ This method had limited application because of the long term deposition of these microspheres in the pulmonary vascular bed. A great stride forward was made in this field following the pioneer work of Benacerraf and others¹ with colloidal albumin. Taplin *et al.*,⁸ and Wagner *et al.*,⁹ working independently, began to use this material labelled with I^{131} for lung scanning in dogs. Following this, many

Nuclear Medicine Clinics, including our own, began using these macroaggregates of albumin for studying lung diseases in patients. These macroaggregates are prepared by controlled heat coagulation of iodinated albumin. For use in lung studies, these aggregates must be larger than capillary size and have averaged about $50\ \mu$ in our work.

It is well recognized that I^{131} possesses but few of the physical properties considered desirable for scintiphotographic studies. We have, therefore, given considerable attention in the past several months to the preparation of albumin labelled with technetium 99m.⁴ Tc^{99m} has a 6 hour half life and is a pure gamma emitter. Its energy of 140 kev. is almost ideal for scintiphotography. Following the preparation of the albumin labelled technetium, production of macroaggregates is carried out by heating. Using this preparation, we are able to administer considerably larger amounts of radioactivity to our patients for better delineation of disease in the lungs.

Studies in our laboratory as well as in many other laboratories have determined that the usual amount of macroaggregates injected for the lung studies is several hundred times below that which will cause even the most minimal of pulmonary embarrassment. Nonetheless, we feel that in cases of acute cor pulmonale, great care must be exercised in the administration of even the small doses of the macroaggregates.

Despite the success which has been achieved in using macroaggregates of albumin for studying lung disease, we feel

* From the Nuclear Medicine Clinic, University of Minnesota Hospitals. Supported by grants from the American Cancer Society (Minnesota Division).

† Associate Professor of Radiology and Director, Nuclear Medicine Clinic.

‡ Medical Fellow, Radiology.

that other radioactive preparations might be more desirable, particularly since the deposition of microemboli in lung capillaries is hardly physiologic. We are, therefore, exploring the use of xenon 133. Xenon gas may be administered into a spirometer and breathed by the patient in a closed system. Thus, the patient may continue to breathe this xenon-air mixture during the time that the scintiphotogram is obtained. Likewise, xenon gas may be dissolved in saline which may be administered intravenously. This provides a method for studying directly the perfusion of the lung by the pulmonary arterial system. In order to use this technique by methods of conventional scintiscanning, it is necessary to use a continuous infusion of xenon-saline preparation. With the scintillation camera, however, we can inject a sufficient amount of xenon to get essentially instantaneous pictures with our scintillation camera. One is justified in administering relatively large doses in excess of 50 mc of xenon 133 without excessive radiation exposure to the patient because of its relatively short effective half life in the body.³

TECHNIQUE

Several points on technique are worthy of mention. It is desirable to view the macroaggregates of albumin with a microscope prior to the time that they are administered to the patient. In this way it may be ascertained that practically all of the particles are at least 10μ in size and that there are very few particles in excess of 100μ . Macroaggregates over 100μ clear more slowly, leading to greater radiation exposure to patients. If the material is prepared in our own laboratory, multiple sterility tests are done and pyrogen free agents are used throughout. Our technique for the preparation of technetium labelled albumin follows rather closely the published work of Stern and associates⁷ with some modifications.⁴

The injection of this material into the patient is likewise very important. In order for the aggregates to be distributed uni-

formly throughout the perfused lung field, the patient should be placed in a supine position prior to administration of the aggregates. Likewise, the patient should be instructed to breathe deeply during the time that the injection is made in order that all potentially available vascular spaces are perfused. Using the scanner, we feel that it is necessary to obtain supine or prone chest roentgenograms, depending on the scanning projection, in order to be able to relate the scan with the roentgenogram since the position of the diaphragms may be considerably different with the patient in the supine as opposed to a standing position. It should be emphasized here that roentgenograms of the chest should be obtained as close to the time of scanning as possible to better evaluate the patient's pulmonary problem.

Some difficulties are encountered in the performance of these studies with the conventional rectilinear scanner. The first of these relates to the length of time that is required for performance of the scan. In our technique a line spacing of 0.3 cm. is used in order to achieve acceptable resolution. We do perform this scan at the maximum speed of our unit, which is 60 cm. per minute; but, nonetheless, the total time required for a single lung scan is more than 1 hour.* This is a rather long time for an ill patient to remain in a fixed position. A second problem relates to the position of the patient which ideally should be such that the scintiphotogram is obtained from the posterior projection in order to better visualize the inferior lung fields. For most scanners, this requires that the patient lie prone. This again is an extremely difficult position for an ill patient who may have respiratory embarrassment to occupy for any length of time.

These two problems are obviated by the use of a scintillation camera. The 11 inch diameter crystal and cylindrical collimator

* This scanner has since been modified to travel at a maximum speed of 120 cm./minute. A third scanner has been purchased which will travel 200 cm./min. Thus, lung scans performed with macroaggregates of albumin labeled with technetium 99m may be completed in 15-30 minutes.

of the camera are very maneuverable so that they can be directed toward the patient, whether the patient occupies a sitting, prone, or supine position. We prefer to obtain scintiphotograms with our camera with the patient in a sitting position so that the results may be compared directly with the conventional posteroanterior chest roentgenogram. Because of the limited size of the field of the scintillation camera, it is sometimes necessary to obtain several projections of the lung in larger patients.

Radiation exposure of patients subjected to lung scintiphotography may be of some concern. Administration of 5 mc of technetium 99m macroaggregates delivers a lung dose of a few millirads as opposed to the lung dose of several hundred millirads when 300 μ c of I^{131} macroaggregates are used.² Using the scintillation camera and doses of technetium 99m up to 5 mc, we are able to obtain scintiphotograms of the lung in a matter of a very few minutes with an acceptable low radiation exposure.

METHOD OF STUDY

The majority of our patient studies to date have been performed by conventional scintillation scanning following an administration of macroaggregates of iodinated albumin. More recently studies have involved the use of technetium 99m macroaggregates and the scintillation camera. Results obtained with either radioisotope or scintiphotographic unit have been found to be comparable. The following evaluation thus relates to all lung scintiphotographic studies performed with macroaggregates of albumin. Reference is also made to preliminary studies with xenon 133.

When conventional rectilinear scanning was employed, the scan was performed with the patient occupying either a prone or supine position. The posterior projection (patient lying prone) was obtained whenever possible for best visualization of the lung bases. Either 300 μ c of the iodinated albumin preparation or up to 5 mc of the Tc^{99m} albumin was administered intravenously with the patient lying down and

breathing deeply as was previously mentioned. Scintiphotograms were obtained immediately thereafter. Multiple projections were usually obtained whenever the scintillation camera was used. Between October 1, 1964 and December 15, 1965, 115 scintiphotograms were obtained on patients at our institution. Seventy-eight of these have sufficient follow-up to be included in this study.

The 78 cases were reviewed to evaluate the relationship of positive or negative scintiphotograms to the roentgenograms, clinical history, and pathologic findings. In all but a few cases, pathologic verification was obtained by autopsy findings, lung biopsy, pulmonary arteriography, cytology, surgery, and bacteriology. Evaluation of the remaining cases was based on clinical and laboratory findings.

For purposes of evaluation, our cases were divided into 4 categories. The first category relates to those patients with an abnormal lung scintiphotogram as well as abnormal chest roentgenograms showing infiltration suggesting infarction, effusion, or decreased pulmonary vasculature in a specific area of the lung fields. The second group includes those patients with positive lung scintiphotograms but no roentgenographic findings suggestive of pulmonary emboli. Studies in Category 3 include those exhibiting negative scintiphotograms but abnormal chest roentgenograms. Finally, the fourth category includes those cases in which both the scintiphotograms and the roentgenograms were negative. This classification follows closely the clinical breakdown according to Quinn and Whitley.⁵

RESULTS

The results of our patient studies have been evaluated by means of the classification previously mentioned and are presented in 4 tables. A scintiphotogram was called abnormal if there was one or more areas of decreased or absent radioactivity. A roentgenogram was called abnormal on the basis of areas of infiltration, loss of vascular pattern in a specific locale, or evi-

dence of pleural effusion. Thus, an abnormal cardiac silhouette was not included in our definition of an abnormal chest roentgenogram. Table I shows that out of a total of 40 patients with abnormal isotope and roentgenographic studies, 19 were determined to be abnormal because of pulmonary embolization and also were thought clinically to have pulmonary emboli. There were no patients in this group of proven pulmonary embolization that presented a clinical picture unlike that seen with embolic deposits in the lung. A summary of all pulmonary problems producing abnormal scintiphotograms and chest roentgenograms is listed in Table I.

Table II summarizes results of studies on 15 patients exhibiting abnormal lung scintiphotograms but normal chest roentgenograms. Eleven of this group were found to have lung emboli. There was a strong clinical impression for embolization in all 11 of these patients. Embolization was found in only 1 patient whose clinical picture was not strongly suggestive for this entity. The other 3 patients in Category II who exhibited little clinical evidence for emboli were found to have either massive cardio-

TABLE I

CATEGORY I (SCINTIPHOTOGRAM—ABNORMAL; CHEST ROENTGENOGRAM—ABNORMAL)

Clinical Impression (+) or (—) for Emboli	Final Diagnosis	No. of Cases (40)
+	Embolization	19
—	Embolization	0
+	a. Carcinoma	2
	b. Pneumonia	3
	c. Congestive heart failure with massive effusion	2
	d. Negative	1
—	a. Carcinoma	3
	b. Pneumonia	6
	c. Atelectasis	3
	d. Polyarteritis nodosa	1

TABLE II

CATEGORY II (SCINTIPHOTOGRAM—ABNORMAL; CHEST ROENTGENOGRAM—NORMAL)

Clinical Impression (+) or (—) for Emboli	Final Diagnosis	No. of Cases (15)
+	Embolization	11
—	Embolization	1
+	—	0
—	a. Massive cardiomegaly	1
	b. Leukemic pulmonary infiltration	1
	c. Hypertensive cardiovascular disease and herpes zoster	1

megaly, leukemic pulmonary infiltrate, or hypertensive cardiovascular disease with complicating herpes zoster.

The 7 patients included in Table III had negative scintiphotograms and positive roentgenograms. Five of these were secondary to pneumonia and metastases. There were 2 patients with a clinical diagnosis of embolization in whom negative scintiphotograms were obtained. These might be considered as possible false negatives except that positive proof of embolization is lacking.

Table IV summarizes the 16 patients included in Category IV. A myriad of pulmonary problems was present, all of which failed to give rise to any abnormalities on

TABLE III

CATEGORY III (SCINTIPHOTOGRAM—NORMAL; CHEST ROENTGENOGRAM—ABNORMAL)

Clinical Impression (+) or (—) for Emboli	Final Diagnosis	No. of Cases (7)
+	Embolization (?)	2
—	a. Pneumonia	4
	b. Metastases	1

TABLE IV
CATEGORY IV (SCINTIPHOTOGRAM—NORMAL; CHEST
ROENTGENOGRAM—NORMAL)

Clinical Impression (+) or (—) for Emboli	Final Diagnosis	No. of Cases (16)
+	a. Bronchopneumonia	2
	b. Pericarditis	1
	c. Bronchiectasis	1
	d. Carcinoma of uterus without tumor emboli	1
	e. Embolization (?)	1
—	a. Postoperative atelectasis	1
	b. Congestive heart failure with effusion (min.)	2
	c. Acute myocardial infarct	2
	d. Gastroenteritis	1
	e. Negative	2
	f. Other than emboli	2

either scintiphotograms or roentgenograms. It is interesting to note that of these 16 cases, only 1 had a strong clinical picture suggesting embolization. However, no positive proof for embolization was obtained.

DISCUSSION

Our evaluation of the 78 cases seems to bear out the impression of other investigators who have shown that patients exhibiting both abnormal scintiphotograms and chest roentgenograms are frequently found to have pulmonary emboli. However, other causes for these studies being abnormal such as bronchogenic carcinoma, pleural effusion, atelectasis and pneumonia are also to be considered. Quinn and Whitley⁶ have also mentioned pulmonary abscesses, pulmonary sequestration, and pleural scars as other causes for abnormal scintiphotograms in patients whose chest roentgenograms are also abnormal. Therefore, if both roentgenogram and scintiphotograms are positive, a definite diagnosis of pulmonary embolization cannot be made without other information. Nonetheless, one may have a high index of suspicion for pulmonary embolization while keeping

in mind the possibility of other etiologic entities as mentioned above.

Twelve of 15 patients with positive scintiphotograms and negative roentgenograms (Category II) were found to have embolization to the lungs. Eleven of these patients also had a clinical diagnosis of pulmonary emboli. The other 3 patients were diagnosed to have massive cardiomegaly, pulmonary leukemic infiltrate and cardiovascular disease, respectively. Thus, the most likely diagnosis in the face of an abnormal pulmonary scintiphotogram and "normal" chest roentgenogram is pulmonary emboli. It must be borne in mind, however, that large pulmonary blebs can also cause positive scans by showing areas of decreased activity. Pulmonary scintiphotography appears to be of greatest value in the evaluation of patients in this group.

The most likely diagnosis of patients with negative scintiphotograms and positive roentgenograms appears to be pneumonia prior to consolidation and/or small amounts of free pleural effusion as seen in upright roentgenograms. In 4 of 7 patients in Category III, the diagnosis of pneumonia was made. Two patients were thought clinically to have pulmonary emboli and were treated medically for this entity. No positive proof of embolization was obtained other than gradual improvement of these 2 patients after institution of therapy.

It appears from Table IV that if both scintiphotograms and roentgenograms are negative, it is unlikely that the patients have pulmonary embolization. A myriad of other cardiac, abdominal, or pulmonary abnormalities was included in this group. The most frequent clinical entity in this group relates to some cardiac problem.

Cases of pleural effusion were somewhat difficult to evaluate because the patients were usually placed either supine or prone during the examination which causes layering out of fluid over the entire hemithorax. If there was a considerable amount of fluid in the hemithorax, the activity would be decreased, perhaps on the basis of some

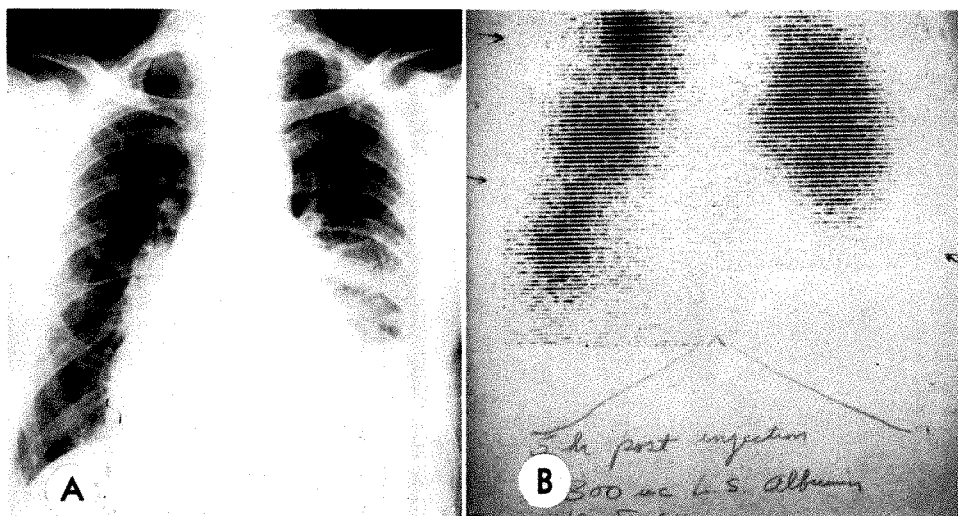


FIG. 1. (A) Posteroanterior chest roentgenogram and (B) lung scintiscan of a 72 year old male. The roentgenogram shows massive cardiomegaly with signs of heart failure but with no abnormalities seen in the right peripheral lung field. The scan using I^{131} macroaggregated albumin shows two areas of decreased perfusion in the right peripheral lung (arrows) and one large area in the left base (arrow).

compromise of vascularity to the affected portion of lung within the fluid or possibly due to some gamma-ray attenuation associated with increased fluid density overlying the lung parenchyma.

We have concluded from the study that the appearance of scalloped or crescent shaped margins mentioned by Wagner *et al.*⁹ is indeed a good sign of pulmonary embolization and areas of complete absence of activity are good indications of pulmonary infarction or possibly pulmonary blebs. Areas of decreased perfusion are also to be strongly suspected as being secondary to embolization or other entities mentioned under Category 1. We do not feel, as does Quinn and Whitley,⁵ that we can rule out pulmonary embolization when there is decreased activity although in this situation pneumonia in the state of consolidation, or atelectasis, are likely etiologies. There are some findings in pulmonary embolization, however, that can be used to differentiate embolization from pneumonia, atelectasis or tumor. It is felt that, in patients with multiple emboli, there will likely be scattered areas of decreased perfusion as opposed to the more likely situation of finding single areas of abnormality in patients with

pneumonia, tumor or atelectasis. Therefore, multiple scalloped areas, indicating decreased and absent areas of perfusion, are considered good evidence for pulmonary embolization.

Three case examples of our experience with macroaggregates of albumin labelled with either iodine 131 or technetium 99m and our early experience with xenon 133 are shown in Figures 1 through 3. The examinations were performed with either a rectilinear scanner or our scintillation camera. Figure 1, A and B illustrates a study on a 72 year old male who had repeated episodes of congestive heart failure over the preceding 7 years. At the time of our present study, the patient experienced the sudden onset of pleuritic chest pain and hemoptysis. The chest roentgenogram (Fig. 1A) shows massive cardiomegaly with pleural effusion bilaterally, with hilar infiltrate on the left, probably signifying congestion and edema. The lung scan (Fig. 1B) shows a marked decrease in activity in the left lower lobe. This scan represents an anterior projection so that this apparent abnormality could be largely due to the patient's cardiomegaly and pleural effusion. In addition, there are two wedge-shaped areas of

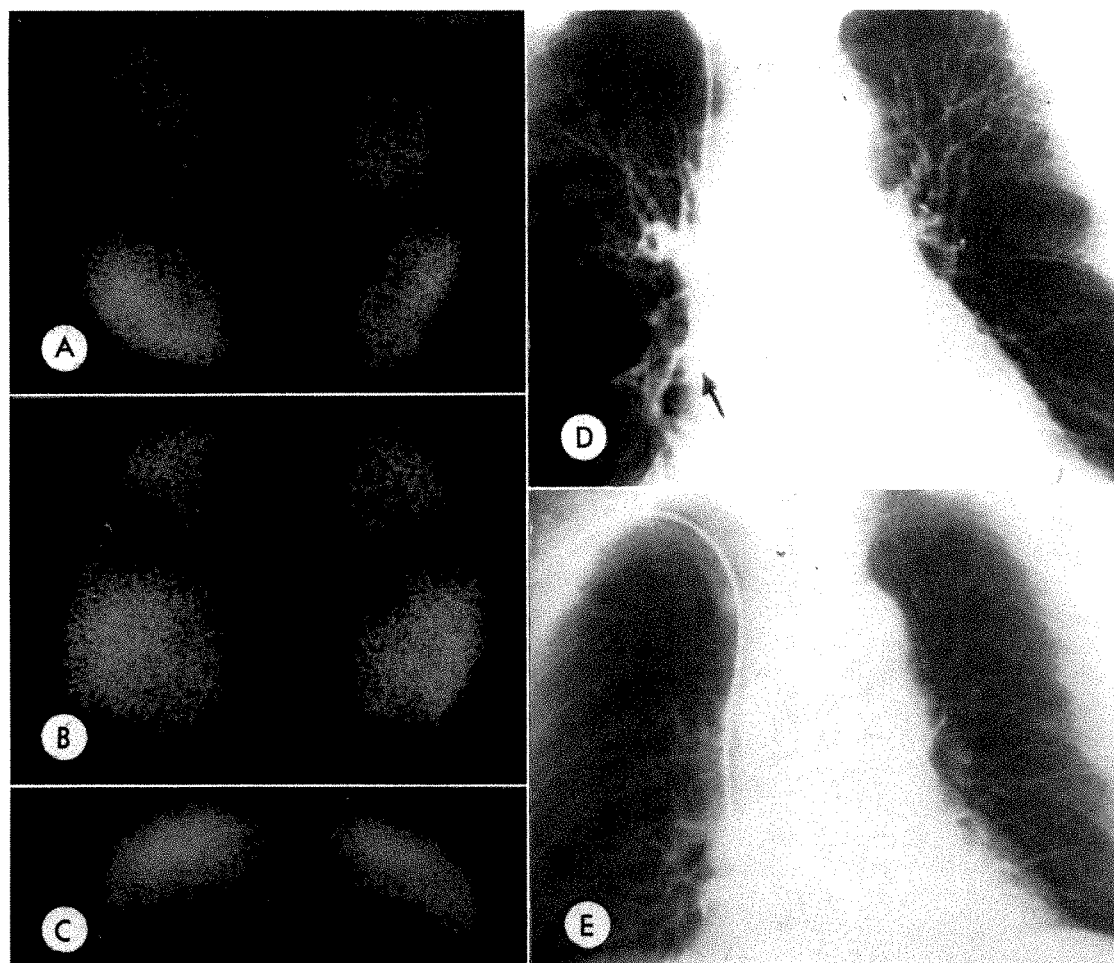


FIG. 2. (*A, B* and *C*) Scintillation camera lung scintiphotos using Tc^{99m} macroaggregated albumin of a 67 year old male showing a marked decrease in perfusion in three areas. The scintiphotos were obtained and are displayed posteriorly, in other words left side is on the reader's left and right side on the reader's right. (*A*) High posterior lung. (*B*) Mid posterior lung. (*C*) Low posterior lung. (*D* and *E*) Two films from a subsequent pulmonary arteriographic study show three areas of delayed perfusion corresponding to those seen on the scintiphotos. (*D*) Arterial phase. (*E*) Venous phase. Arrow in *D* points out a portion of a large saddle embolus.

decreased activity in the right peripheral lung field, scalloping the margins in a manner described previously. A chest roentgenogram obtained 7 days after the onset of chest pain showed an area in the right peripheral lung field consistent with infarction. A decrease in the size of the wedge-shaped areas on the right was noted on subsequent lung scans but at no time did these completely disappear. It is our conclusion that these areas did represent decreased perfusion secondary to pulmonary emboli.

Figure 2, *A-E* shows studies on a 67 year old male whose only complaint was the sudden onset of severe dyspnea with no other symptomatology. He had had similar episodes of dyspnea 1 year prior to the present event, at which time he had thrombophlebitis. The plain chest roentgenograms were interpreted as normal. The patient then received 5 mc of technetium 99m tagged to macroaggregates of albumin followed by scintiphotos (Fig. 2, *A, B* and *C*) obtained with our scintillation camera. Three areas of decreased activity,

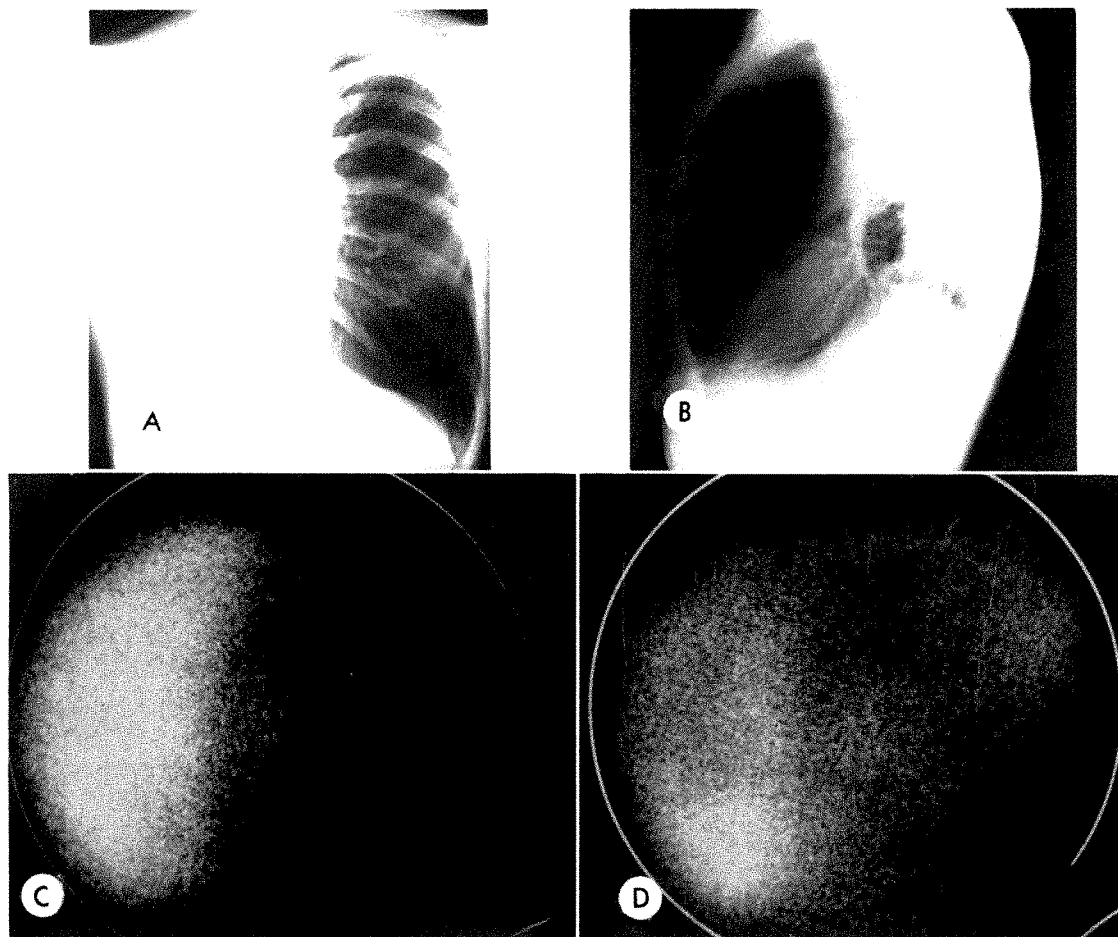


FIG. 3. (*A* and *B*) Posteroanterior and lateral chest roentgenograms and (*C* and *D*) scintillation camera scintiphotograms obtained on a patient being evaluated for progressive dyspnea. The roentgenograms show consolidation of the right hemithorax with lucent areas of bronchiectasis. There is a large radiolucent area visible in the left base representing a bulla. The scintiphotograms were obtained and are displayed posteriorly, in other words, left side is on the reader's left and right side on the reader's right. They were taken using xenon ^{133} which was administered by inhalation. *C* was taken during inhalation and demonstrates ventilation of the left lung only. *D* was taken after the xenon inhalation was discontinued and shows clearance of the isotope, primarily by the left lung, with some increased activity in the region of the large bulla.

two involving the midportions of both lungs and one involving the right apex, are seen. Because of this study, pulmonary arteriograms were obtained (Fig. 2, *D* and *E*) which show delayed perfusion to the same areas where decreased activity was seen on the scintiphotograms, as well as a saddle embolus involving both pulmonary arteries. This embolus was found at surgery to have markedly attenuated the lumen of the arteries to the right apex, right midlung field, as well as left midlung field.

Figure 3, *A-D* illustrates the use of xenon ^{133} inhalation to study pulmonary function and perfusion with our scintillation camera. This patient was being evaluated for progressive dyspnea. Chest roentgenograms (Fig. 3, *A* and *B*) show an opacification of the right hemithorax with a mediastinal shift to the right. Radiolucencies in the right upper lobe relate to areas of bronchiectasis. The left lung field appears relatively normal except for an area of increased radiolucency in the left lower lung

field. This study was performed using a re-breathing system which involved the use of a spirometer containing 5 liters of air to which 5 mc of xenon 133 gas had been added.

The initial scintillation camera study (Fig. 3C) was obtained several minutes after starting inhalation of the xenon-air mixture. There appears to be good ventilation of the left lung as evidenced by the high content of radioactivity recorded on the scintiphotogram. There is essentially no ventilation on the right side. Another scintiphotogram (Fig. 3D) was obtained 3 minutes after the patient had stopped breathing the xenon-air mixture. This shows some decrease in activity in most of the left lung field, indicating the gradual clearance of the xenon 133 from body tissues. There is a notable persistence of radioactivity in the left lower lung in the region of the lucency seen on the chest roentgenograms which represents a large bulla. The right lung field remains inactive except for a small amount of xenon 133 gas trapped in the bronchiectatic areas of the right upper lung which indicates some perfusion of this area of lung.

Several other patients have also been studied with xenon 133 gas and the scintillation camera in the manner described above. Results have been uniformly satisfactory. In addition, 2 other patients have been studied by intravenous administration of xenon 133 dissolved in saline. More than 90 per cent of the xenon is cleared in one passage to the lungs. Using 5-10 mc, it is possible to obtain adequate scintiphotograms with the scintillation camera. The initial distribution relates closely to pulmonary perfusion as is also seen in studies with macroaggregates of albumin.

SUMMARY

Scintiphotograms of the lung using macroaggregates of albumin tagged with iodine 131 and technetium 99m were obtained on 115 patients. Seventy-eight of these have had sufficient follow-up to be included here. The dose administered in-

travenously was 300 μ c in patients receiving the iodine 131 macroaggregates of albumin and up to 5 mc in patients receiving technetium 99m macroaggregates of albumin. The macroaggregates ranged in size from 10 to 100 μ . These studies have indicated the sites and magnitude of pulmonary arterial obstruction whether they were recognizable roentgenographically or not. Areas of decreased activity on the scintiphotograms relate to areas of ischemia, which are frequently due to pulmonary embolization but also can be secondary to pneumonia, atelectasis, emphysematous blebs, abscesses and cysts.

We have used either a rectilinear scanner or scintillation camera for these studies. The two major disadvantages of rectilinear scanning relate to the time required to perform the scan and, secondly, to the prone positioning of the patient, which is desirable for best results but is difficult to obtain, particularly if the patient is severely ill. The scintillation camera obviates these problems but has the disadvantage of a restricted field size, making it necessary to obtain several studies in large patients.

Scintiphotography of the lungs using macroaggregates of albumin is considered to be an excellent screening test prior to subjecting a patient to pulmonary angiography. Serial scintiphotograms can be very helpful in following closely disease processes within the pulmonary parenchyma. We are presently exploring the use of xenon 133 for studies of pulmonary function and perfusion. Preliminary results indicate that xenon 133 offers significant advantages over the use of macroaggregates, providing a device such as the scintillation camera is available for obtaining the scintiphotograms.

Merle K. Loken, M.D.
Nuclear Medicine Clinic
University of Minnesota Hospitals
Box 187
Minneapolis, Minnesota 55455

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RADIOISOTOPE SCINTIPHOTOGRAPHY WITH TECHNETIUM 99m AND THE GAMMA SCINTILLATION CAMERA*

By ALEXANDER GOTTSCHALK, M.D.

CHICAGO, ILLINOIS

IN RECENT years, considerable progress has been made in nuclear medicine, instrumentation in particular having witnessed some ingenious new developments. One example of this is the scintillation camera developed by Anger, which makes possible the rapid imaging of isotopes without mechanical scanning. This instrument, continuously sensitive to its entire field of view, operates in the following manner: A pinhole or multiaperture collimator first projects the gamma ray onto a large ($11 \times \frac{1}{2}$ inch) sodium iodide crystal. Upon interaction with the crystal, the gamma ray produces flashes of light that are detected by a hexagonal array of 19 photomultiplier tubes which view overlapping areas of the crystal. The voltage pulses from the phototubes are fed into a resistor matrix which acts as an analog computer and codes the location of each incident photon. This information is transmitted by means of X and Y positioning signals to the face of an oscilloscope. A third lead, the Z lead, sums all of the voltage pulses received, and therefore is proportional to the initial gamma-ray energy. The Z lead goes to a pulse height analyzer, and then to the grid of the cathode-ray tube. If the energy is appropriate, the grid is turned on and a white dot appears on the oscilloscope face in a position that corresponds to the interaction of the initial photon with the crystal. By making a timed exposure of the oscilloscope face, photographic integration is achieved and the distribution of the radioisotope within the source results. Exposures last from a second to a few minutes, as many as

700,000 flashes being recorded in this interval. A detailed discussion of this instrument is available in the literature.^{1,2,5}

Equally impressive advances in nuclear medicine have seen the development of nuclides for radioisotope scanning (imaging) and other uses. One of the newest of these nuclides is technetium 99m.⁸ The physical characteristics of this isotope are highly desirable. It has a short physical half life of 6 hours, a clean 140 kev. gamma ray, and an absence of primary particle radiation, and can, therefore, be administered in millicurie amounts with minimal radiation to the patient. For example, assuming no excretion, and generalized distribution, 1 mc of technetium 99m as pertechnetate gives a whole body dose of about 10 millirads. The dosimetry of technetium for a variety of organs and chemical forms has been calculated elsewhere.^{9,15}

Although the 140 kev. technetium gamma ray is penetrating enough to be used to scan organs at depth (half value layer = 4.5 cm. of tissue), it is soft enough to be easily collimated. Complete shielding is achieved by one-fourth inch of lead, and it is 100 per cent absorbed in a one-half inch sodium iodide crystal.⁹

By combining the imaging properties of the gamma scintillation camera with the high count rates available from technetium 99m, it is possible to solve some of the problems inherent in conventional rectilinear scanning with other agents. For example, with technetium 99m the exposure time per view is reduced from as high as 45 minutes to 1 to 2 minutes or less. Consequently, it is

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From the Department of Radiology, University of Chicago, and Argonne Cancer Research Hospital (operated by the University of Chicago, for the United States Atomic Energy Commission), Chicago, Illinois.

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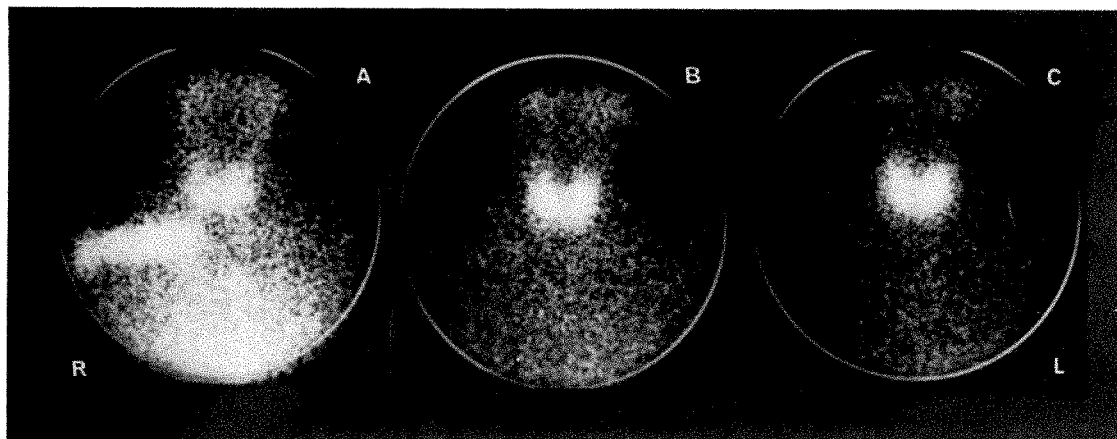


FIG. 1. Serial 1 minute scintiphotographs using 1 mc of Tc^{99m} pertechnetate. The patient had Graves' disease which was incompletely controlled with propylthiouracil (T_3 resin sponge test well into hyperthyroid range). (A) 0-1 minute after injection in the right antecubital vein. The bolus of pertechnetate can be seen in the axillary vein. Thyroid trapping is already evident. Note the salivary gland uptake. The white circle is the field of view. (B) 3-4 minutes. (C) 7-8 minutes. These show a progressive increase in thyroid trapping of pertechnetate, with decrease in body background.

possible to extend the range of patients examined to include young children as well as adults who otherwise would be unable to cooperate. In addition, the routine use of oblique, lateral, anterior, and posterior views is now practical, thus increasing the diagnostic potential of the study.⁴ Finally, the use of short lived nuclides permits a higher efficiency of utilization of the administered dose without subjecting the patient to needless irradiation for days or perhaps weeks after injection of the scanning agent, and supplementary isotope studies can easily be performed within a short time.

In this paper the various compounds of technetium 99m that have been prepared at the University of Chicago are described and the improved examinations that result when these agents are used with the gamma scintillation camera are illustrated.

THYROID

Technetium 99m as the pertechnetate is obtained by an ion exchange process from its 2.8 day half life parent molybdenum 99 (Mo-Tc isotope cow). Pertechnetate has a body distribution similar to iodide. Like iodide, it is trapped in the thyroid, but unlike iodide, it is not organified. Conse-

quently, it can be used to study the thyroid trapping mechanism (Fig. 1, A, B and C), and also as a thyroid scanning agent with optimum visualization 30 to 60 minutes after intravenous injection.⁹

BRAIN

Pertechnetate localizes essentially in the extracellular space, and, consequently, has the same brain scanning potential as such agents as the positron emitting gallium 68 EDTA.⁷ In animal experiments, "tumor/brain" ratios of pertechnetate are comparable to those obtained with neohydrin.¹² In our institution, routine brain scanning is done with the specially constructed Argonne Cancer Research Hospital brain scanner, which permits optimal simultaneous paired views of the brain to be taken in 15 minutes, and usable scans as rapidly as 90 seconds if necessary.³ However, the scanner is built so that the patient must lie on his side for the frontal and posterior views, and thus an occasional patient is unable to cooperate. Under these circumstances, it is still possible to exploit the rapid imaging of the scintillation camera to complete the examination. An example of a brain scintiphotograph is shown in Figure 2.

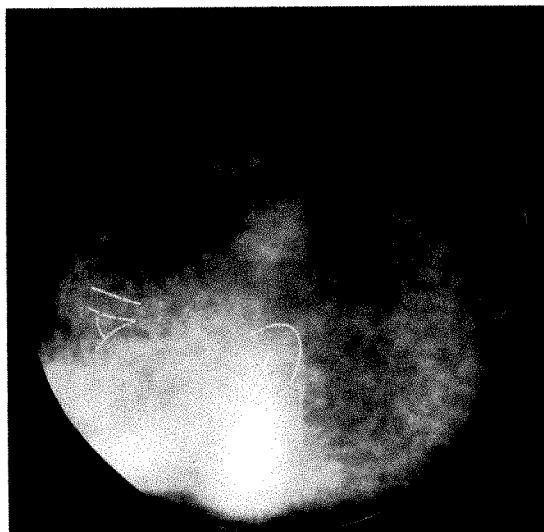


FIG. 2. Lateral view of a well circumscribed left mid-parietal lesion. The 3 minute exposure (100,000 dots) was started 10 minutes after intravenous injection of 2 mc of Tc^{99m} pertechnetate.

RETICULOENDOTHELIAL SYSTEM

The phagocytosis of large particles by reticuloendothelial cells is the basis for the use of radioactive colloidal suspensions for liver, spleen, and bone marrow scanning. The sulfur colloid of technetium 99m is prepared by adding hydrogen sulfide gas to an acidified solution of pertechnetate, and

stabilizing with a freshly prepared gelatin suspension. The resultant mixture is neutralized and passed through a sterilizing filter to yield particles of 0.22μ . A detailed description of the procedure is published elsewhere.^{9,10}

Animal studies show that approximately 5 per cent of the sulfur colloid is fixed in the bone marrow, 5 to 10 per cent in the spleen, and virtually all of the remainder in the liver. It should be noted, however, that the liver and spleen contain equal quantities of colloid on a weight basis. The sulfur colloid has been used successfully for studying all three of these organs. With a 2 to 3 mc dose, it is possible to get count rates in excess of 500,000 per minute for liver and spleen scanning (see Fig. 3 through 5). Since we routinely collect 200 to 400 thousand counts per minute for a single scintiphotograph, it is possible to finish an examination while the patient holds his breath. Even if the subject is quite ill, it is still reasonable to expect him to hold his breath for 15 to 20 seconds. The exposure is then stopped while the patient rests. He is then asked to hold his breath again and to return to the original phase of respiration. The exposure is then continued. This process is repeated until the desired number of counts is accu-

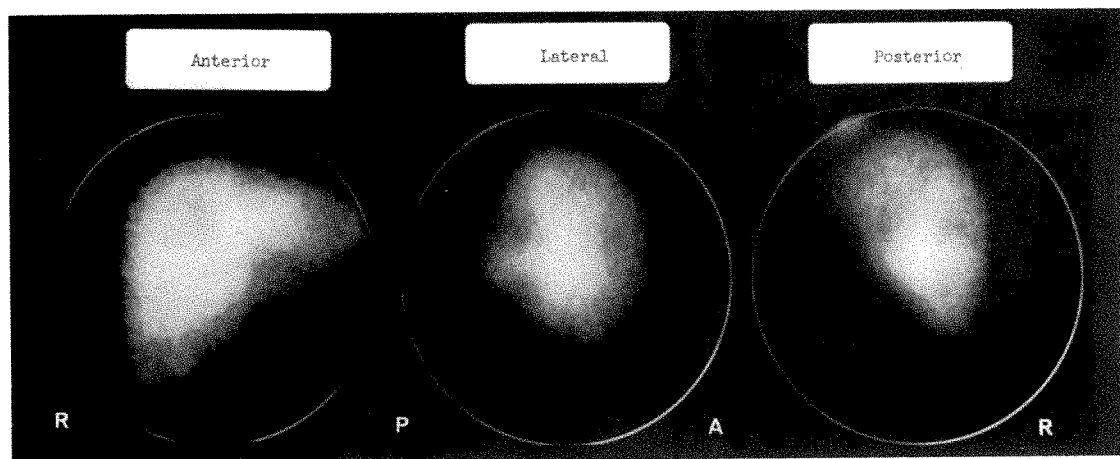


FIG. 3. Liver scintiphotographs using 2 mc of Tc^{99m} sulfur colloid. The study was started 5 minutes after injection. The exposure times were about 1 minute, and 400,000 dots were collected per picture. Widespread colon metastases are demonstrated. Note how many lesions would be missed if only a single frontal view was obtained. The sharply defined edges on the anterior projection are due to the suspended respiration (see text). This technique makes it possible to identify clearly small metastases such as those seen on the medial inferior border of the right lobe, which are virtually obscured by respiration.

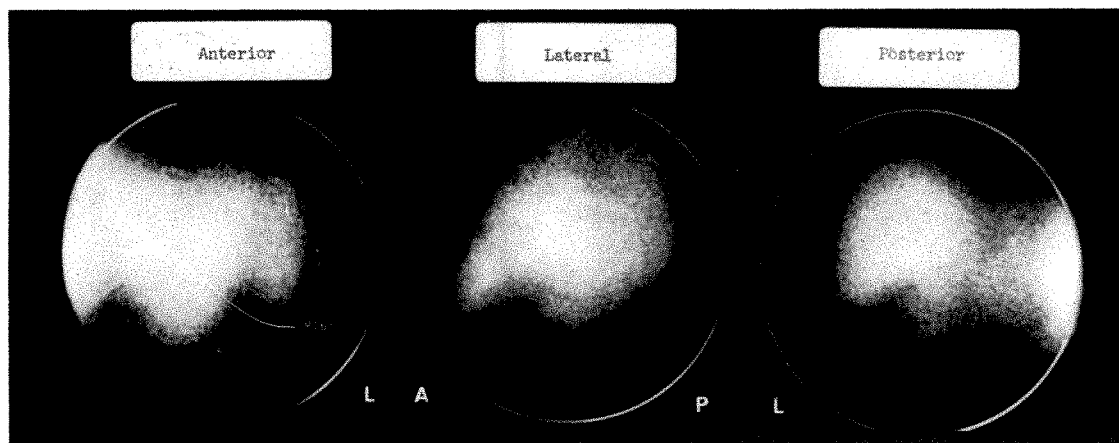


FIG. 4. Scintiphotographs of the left upper abdomen with 2 mc of $\text{Tc}^{99\text{m}}$ sulfur colloid. Exposure times of 2 to 3 minutes were used with 300,000 dots collected per view. Clinically, a mass was palpable in the left upper abdomen, and splenomegaly was suspected. The study shows that the palpable mass was in fact the left lobe of the liver (single arrow). The spleen, however, is prominent in the anterior view (double arrow), overlaps the liver in the lateral view, and is larger than normal in the posterior view. Consequently, splenomegaly is present as well (compare to Fig. 5 A).

culated. This is a simple but effective method for avoiding the resolution loss caused by respiratory motion. Quantification of the motion artifact has demonstrated

that breathing doubles the resolution loss with the scintillation camera, and triples it with a good scanning system.⁶ In spite of the large dose administered, radiation to

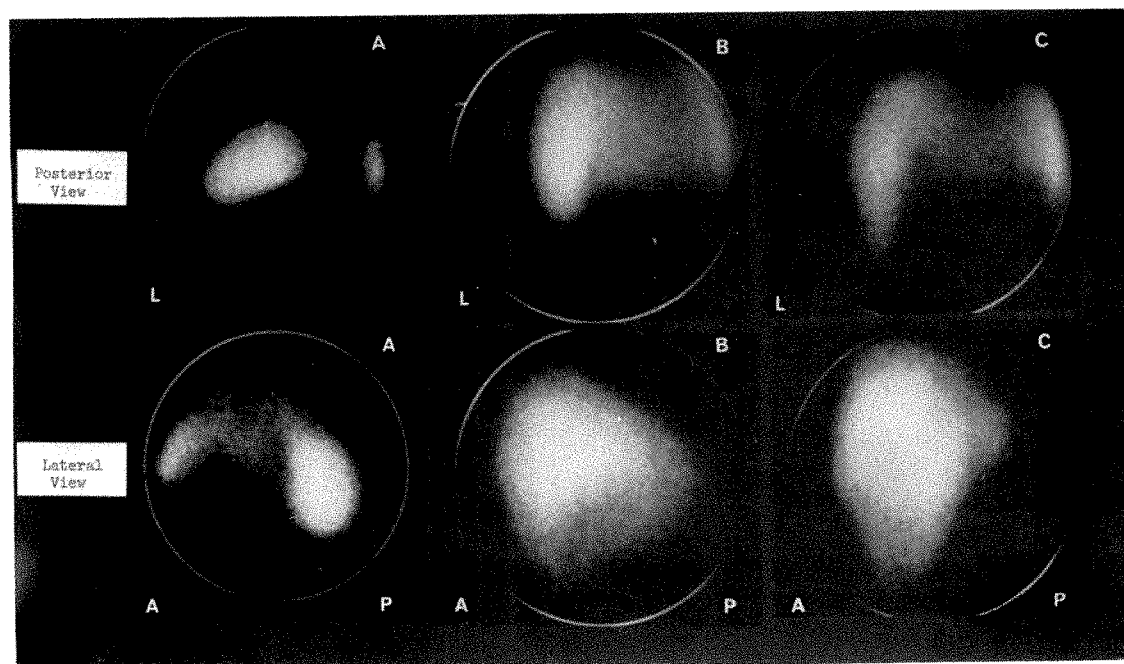


FIG. 5. Splenic scintiphotographs using 2 mc of $\text{Tc}^{99\text{m}}$ sulfur colloid and about 1 minute exposure times (300,000 to 400,000 dots collected). (A) Normal adult spleen. (B) Ten year old child with Hodgkin's disease and a non-palpable spleen. It is clearly enlarged. Note that the spleen cannot be separated from the liver in the lateral view (see text). (C) Fourteen year old patient with Hodgkin's disease and a palpably enlarged spleen.

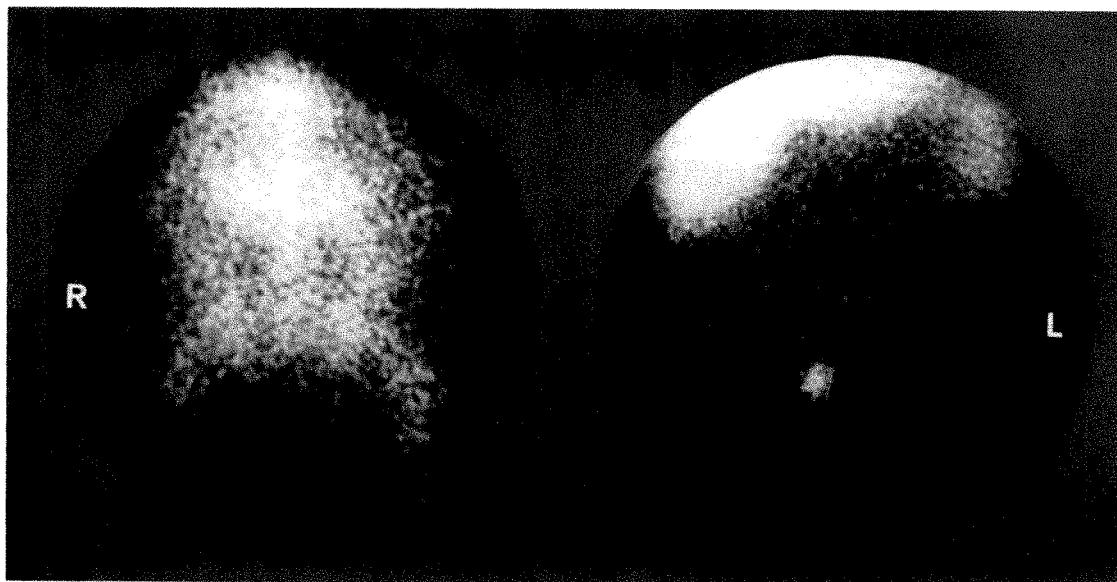


Fig. 6. Bone marrow scintiphotographs using 0.5 mc of Tc^{99m} sulfur colloid. *Left*: Pelvis of a 6 year old child with acute leukemia in remission; the marrow uptake and distribution are normal. *Right*: Pelvis of a 1½ year old infant critically ill with acute leukemia. The bright dot in the lower portion of the picture is an external marker source (Co^{57}) placed over the pubis. The lower edge of both liver and spleen is seen at the top of the scintiphotograph. No marrow uptake is visible. Subsequent biopsy showed the marrow to be completely replaced by leukemic infiltrate.

the patient is low. Assuming permanent fixation of the colloid, the liver receives about 300 millirads, the spleen 150 millirads, the bone marrow 30 millirads per mc of sulfur colloid intravenously injected.

The use of technetium sulfur colloid as a combined liver and spleen scanning agent has proved to be an asset.¹⁴ Frequently, it is clinically important to evaluate left upper quadrant masses (Fig. 4) and it is helpful to have both liver and spleen visualized simultaneously. Since the normal spleen is posterior, it is usually poorly visualized in the anterior view because tissue attenuation of the gamma rays is maximum. In the lateral view, the normal spleen is readily separated from the liver, which is anterior to it. The spleen is best seen, of course, with a posterior projection. When the spleen is enlarged, not only is this evident on the posterior projection, but it is no longer possible to separate liver from spleen on the lateral projection. In some cases, the spleen becomes large enough to show the same activity as the nearby left lobe of the liver on the frontal projection, and extends below

the costal margin. Using these criteria, we have demonstrated definite splenomegaly before the spleen becomes clinically palpable (see Fig. 5, A, B and C).

While bone marrow scanning using the technetium 99m sulfur colloid has, as yet, limited clinical value, it is occasionally helpful in determining the extent of marrow-replacing disorders such as acute leukemia (Fig. 6). A basic assumption in the use of a colloidal preparation for bone marrow scanning is that the marrow reticulo-endothelial system is comparable in distribution to the marrow erythropoietic system. This remains to be proved, but proof might be possible by correlating the distribution of nuclides such as positron emitting iron 52¹⁶ with colloidal preparations.

KIDNEY

A technetium iron complex has recently been prepared by reducing an acidified solution of pertechnetate with ascorbic acid and adding ferric chloride. The mixture is neutralized and passed through an ion exchange resin to remove unreacted

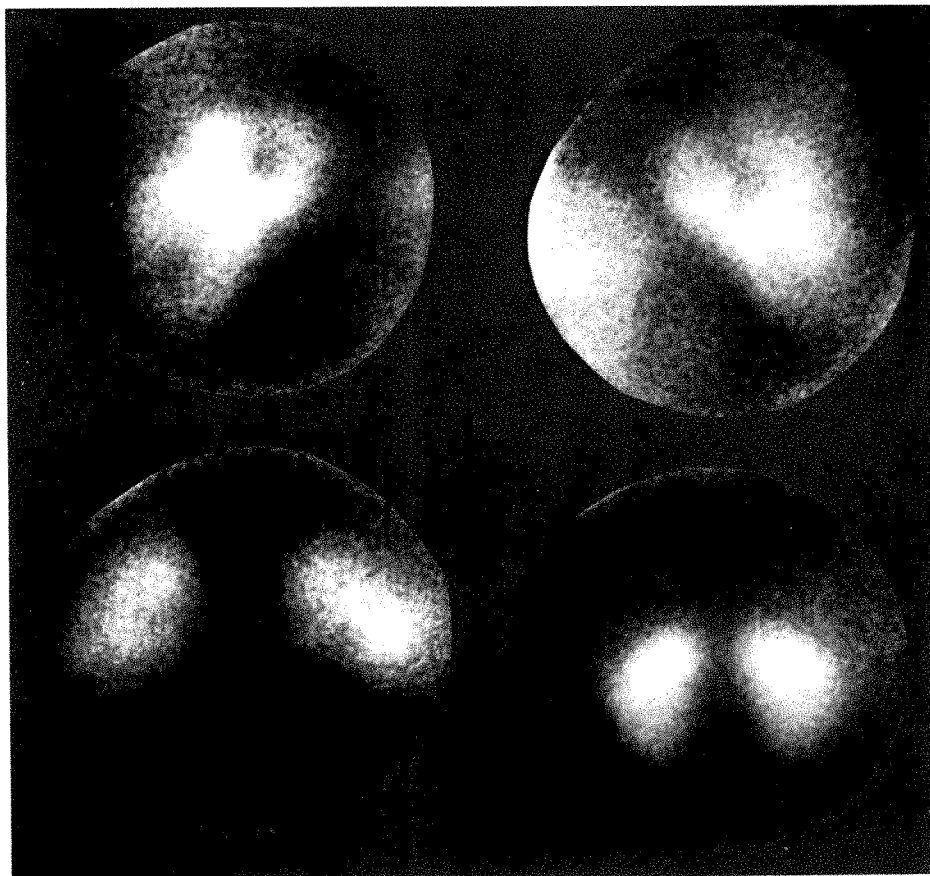


FIG. 7. Kidney scintiphotographs with 1 mc of $\text{Tc}^{99\text{m}}$ iron complex. Exposure times of 4 to 5 minutes were used with 200,000 dots collected. *Top row:* Oblique views of left and right kidney of a 44 year old woman with known polycystic disease. The scintiphotographs were taken 5 hours after intravenous injection. The patient is the mother of 2 children whose scintiphotographs appear in the bottom row. *Bottom left:* Prone view at 1 hour of 17 year old son with strong suspicion of beginning cyst formation. *Bottom right:* Prone view at 1 hour of 6 year old daughter with normal kidneys.

pertechnetate. In animals, 50 to 75 per cent of the iron complex is rapidly excreted in about 1 hour; the rest has a biologic half time of about 18 hours.¹¹ Although this material is, as yet, incompletely characterized chemically, radioautographic studies indicate that some of it is fixed in the renal cortex. It is, therefore, an excellent renal scanning agent. Human excretion studies

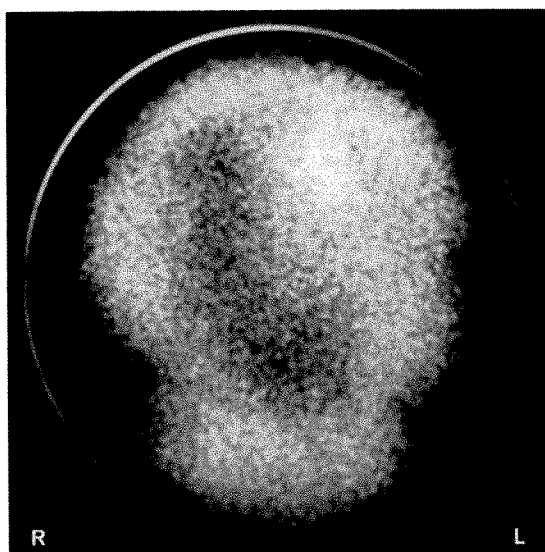


FIG. 8. Placenta scintiphotograph with 1 mc of $\text{Tc}^{99\text{m}}$ albumin. A placenta previa was suspected clinically, and could not be excluded by roentgenograms. The scintiphotograph clearly localizes the placenta to the left upper quadrant of the uterus.

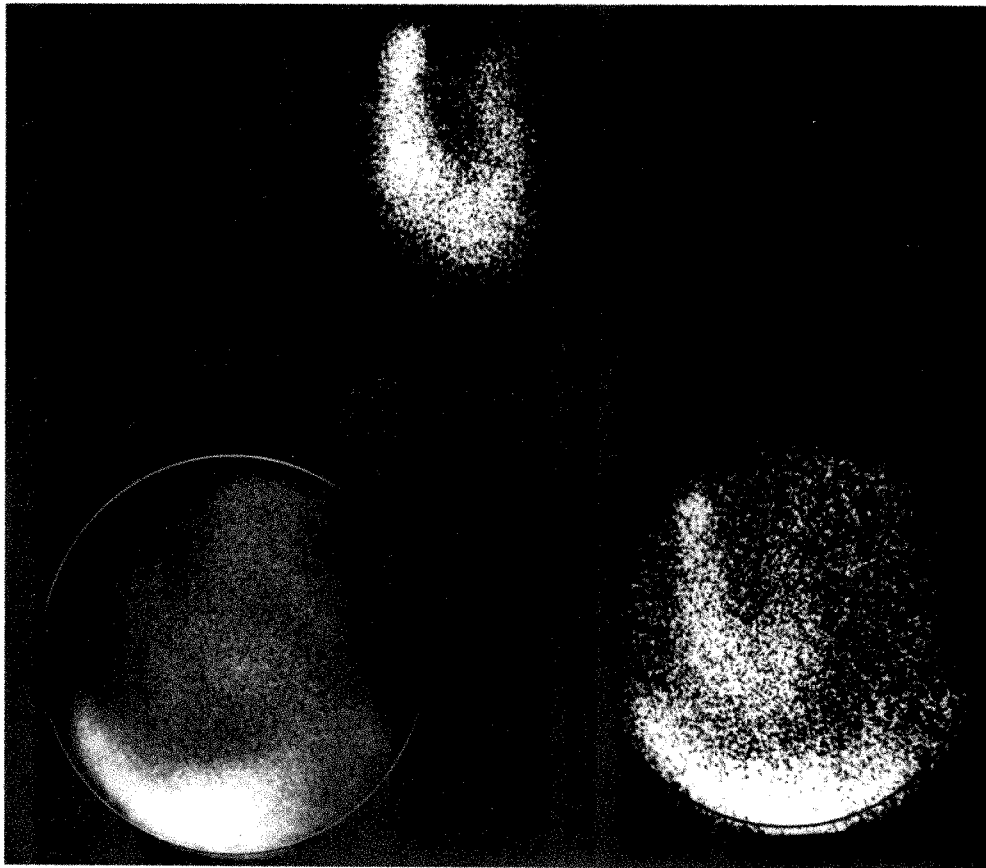


FIG. 9. Multiple organ scintiphotos for the diagnosis of pericardial effusion. *Top:* 0-15 seconds after the injection of 1 mc of Tc^{99m} sulfur colloid. The superior vena cava, right heart blood pool, and pulmonary outflow tract are seen. *Bottom left:* Scintiphoto after administration of 1 mc of Tc^{99m} macroaggregated albumin (MAA). The superior and lateral pericardium is outlined by the left lung MAA, the inferior and lower right pericardium by the radiocolloid in the liver. The heart blood pool is visualized by residual pertechnetate in the MAA preparation. The clear space around the heart blood is a pericardial effusion. (This was confirmed with angiocardiography and responded promptly to diuretics.) *Bottom right:* 15 second scintiphoto after injection of Tc^{99m} albumin to reconfirm the location of the heart blood pool, and also to redemonstrate the space between the liver and the heart blood.

show that about 25 per cent is retained by the kidneys (half time=9.5 days); while the rest is rapidly excreted (half time 4 to 5 hours), virtually all the excreted radioactivity is found in the urine. Assuming a constant 10 per cent renal concentration of the rapidly excreted portion, the dose to the kidneys is less than 500 millirads per mc. One millicurie of this agent gives count rates of up to 50,000 per minute, 1 hour after intravenous administration. As a result, renal scintiphotos are made with only a few minutes' exposure. Examples are shown in Figure 7.

BLOOD POOL SCANNING

A method for preparation of technetium albumin has been described by McAfee and co-workers,¹³ and a similar method is in use in our laboratory. The use of this agent makes localization of such organs as the placenta possible by scanning (Fig. 8). This represents an advance over the previous methods of localization that relied exclusively on counting with a scintillation probe.

MULTIPLE ORGAN SCANNING

This new technique has been used to

diagnose pericardial effusion. With conventional methods, it is customary to make a scan of the heart blood using agents such as RISA, or I^{131} cholografin. Without moving the patient, a 6 foot chest roentgenogram is exposed and is correlated with the scan. In practice, it is sometimes hard to identify borders of the scan, so that comparison of the size of the heart blood pool and the cardiac silhouette is difficult.

Accordingly, a procedure has been devised wherein a pericardial effusion is outlined on the scintiphotograph itself without resorting to superimposition on a roentgenogram. This is accomplished by first locating the liver with technetium sulfur colloid. The lungs are next identified with a macroaggregate of technetium albumin. Finally, the heart blood pool is visualized with technetium albumin. In short, the outer surface of the heart is outlined inferiorly by the liver, and superiorly and laterally by the lungs. Consequently, a discrepancy between the size of the heart blood pool and surrounding organs can only represent pericardial thickening or effusion. An example is shown in Figure 9.

SUMMARY

The physical properties of technetium 99m allow millicurie quantities to be administered to a patient without radiation hazard. Its clean 140 kev. gamma ray makes it an ideal agent for use with the scintillation camera. Count rates as high as 700,000 per minute are achieved and consequently, multiple views can easily be obtained, thus enhancing diagnostic accuracy. It is now possible to use exposures so short that they can be made while the patient holds his breath. This eliminates the resolution loss caused by respiration in scanning moving organs such as liver and spleen. Several chemical forms of technetium are now available for radioisotope imaging. These include pertechnetate for thyroid and brain; sulfur colloid for liver, spleen and marrow; iron complex for kidney; albumin for blood pool; and aggregated albumin for lung. Examples of the clinical

use of these agents with the gamma scintillation camera are described.

950 East 59th Street
Chicago, Illinois 60637

The clinical results presented are the product of continuing investigations in nuclear medicine at the University of Chicago. The cooperation and support of my colleagues in nuclear research—Dr. P. V. Harper, Mrs. K. A. Lathrop, Mr. R. N. Beck, and Mr. D. B. Charleston—made these studies possible. Thanks go to Miss Vivian Reynolds and Miss Violet Stark for technical assistance.

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THYROID SCANNING USING THE GAMMA CAMERA*

By YEN WANG, M.D., D.Sc. (MED.)†
PITTSBURGH, PENNSYLVANIA

ANGER's gamma camera^{1,2} has been used generally in dynamic studies and large organ scanning. Recently, the contrast and the detail resolution of this device have been tested. This is carefully documented in a report by Becker and associates.² In their experimental set-up with phantoms, they achieved a detail resolution of about 0.5 cm. by using optimum contrast and a sufficient number of dots. The size and brightness of the dots were also carefully selected. They have found that the best utilization of the gamma camera's capability to produce maximum contrast resolution at the six contrast degrees requires 364 dots/cm.² of the inspected area of the organ. The exposure times may run from a few minutes to several minutes, depending on the amount of radioactivity which accumulates in the organ in order to produce sufficient picture quality. In studying function, the general resolution is not so important, and each individual dot should be distinct on the photograph. Factors governing the intensity and size of the dots must be carefully selected according to the desired degree of resolution. The same intensity with a low resolution for a function study would lead to overexposure on high resolution photographs for morphologic evaluation of the thyroid gland.

We have used the gamma camera approximately 4 months and have observed that the degree of contrast has changed. It is now necessary to use about a 10 to 15 per cent higher contrast.

MATERIAL AND METHOD

The present study was carried out with a Picker thyroid phantom, a 3 by 2 inch iodide crystal Magnascanner, and Anger's

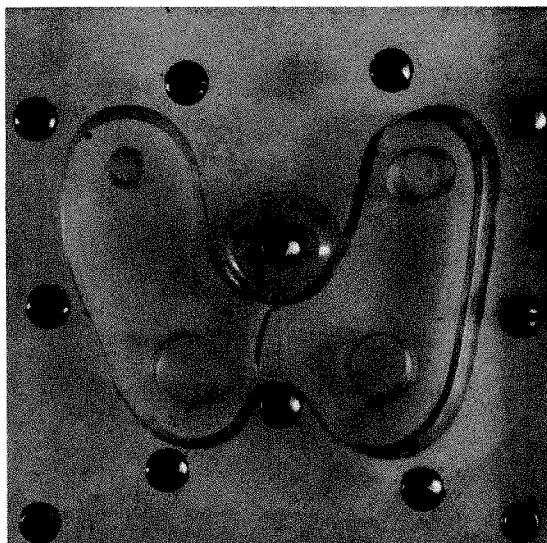


FIG. 1. A Picker thyroid phantom with filling defects was filled with 25 μ c of I^{131} .

gamma camera. Two patients presenting with thyroid nodules were studied.

The thyroid phantom was filled with 25 μ c of I^{131} . This was scanned first with the 3 by 2 inch iodide crystal mechanical scanner and a 31 hole lead focusing collimator. The scanning factors were: maximum counting rates—4,500 cpm., time constant $\frac{1}{8}$ second, dot 16, range differential 40, background cut-off 40 per cent and scan speed 27 cm./min. The total scanning time was about 12 minutes.

RESULTS

Figure 1 shows the Picker thyroid phantom with the various filling defects. It has been used for testing resolution and optimal scanning factors.

Figure 2 is the dot scan. The hot lobe on the left side contains a distinct cold nodule (measuring about 1.2 cm. in diameter) in the lower pole and another small,

* From the Departments of Radiology, University of Pittsburgh School of Medicine, Presbyterian-University Hospital and St. Francis General Hospital, Pittsburgh, Pennsylvania.

† Associate Professor of Radiology, University of Pittsburgh School of Medicine, Presbyterian-University Hospital, Pittsburgh, Pennsylvania.

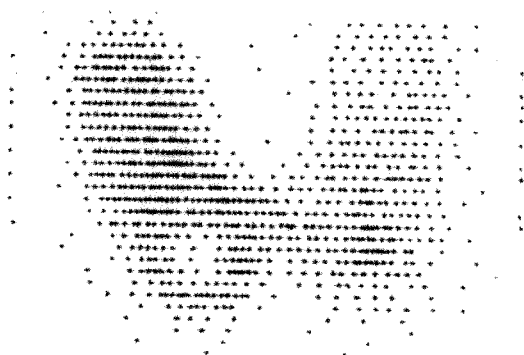


FIG. 2. A dot scan of the phantom shown in Figure 1. The various filling defects are demonstrated. The scanning technique is described in the text.

relatively cool, nodule in the upper pole. On the right, a slightly cool lobe shows a distinct hot nodule in the lower pole (measuring about 1.2 cm. in diameter) and another smaller, relatively cool, nodule in the upper pole. Figure 3, the photoscan of the same phantom, clearly demonstrates the various filling defects in the thyroid phantom.

The same phantom was used to test the scintillation camera with a single pinhole collimator. Some essential factors regarding better resolution were tested. From experience, a fine dot technique was used because we desired good resolution. Figure 4 demonstrates the resolution changes in 3

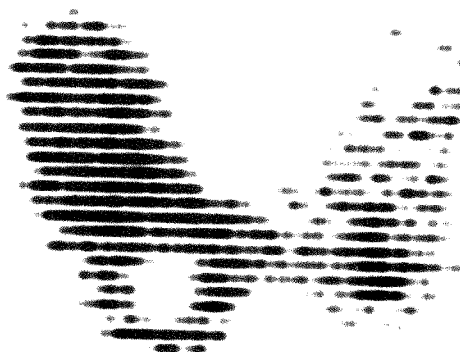


FIG. 3. A photoscan of the phantom shown in Figure 1. The various filling defects are more clearly demonstrated than on the dot scan of Figure 2. The scanning technique is described in the text.

different count ranges at the imaging size of 1.5 and an intensity factor of 290. The film was exposed about 3 minutes. The accumulation of count is a function of the time. The best resolution was obtained with 30,000–60,000 counts per study. The difference between the two lobes and the various filling defects are well demonstrated. Figure 5 illustrates resolution changes, occurring at about 40,000 counts per study, with 3 different imaging sizes, 1, 1.5 and 2. The imaging size can be set by means of a dial on the machine. As can be noted, the imaging size of 2 is too large for

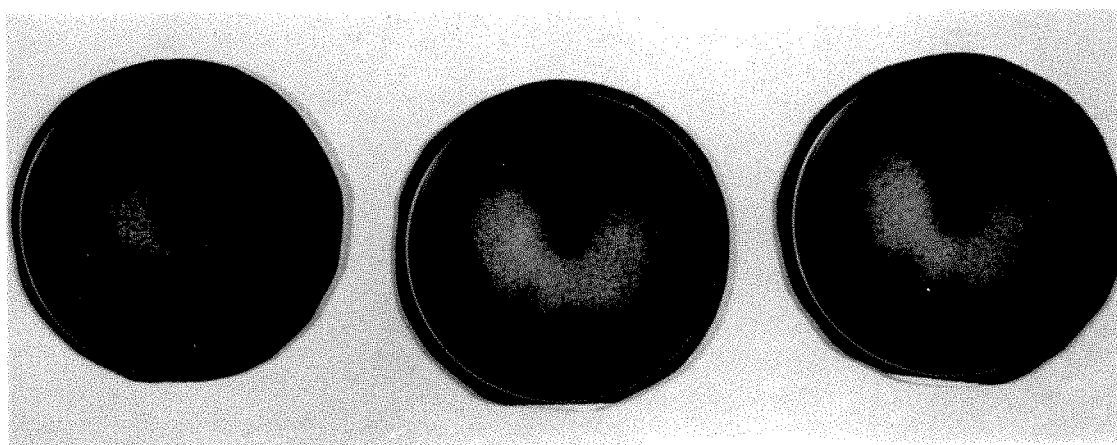


FIG. 4. Pictures of the same phantom with the same radioactivity are taken with the Anger camera. *Left:* 40,000 counts; *middle:* 60,000 counts; and *right:* 80,000 counts per study. The defects in the phantom are seen with various degrees of resolution, depending on the counts used.

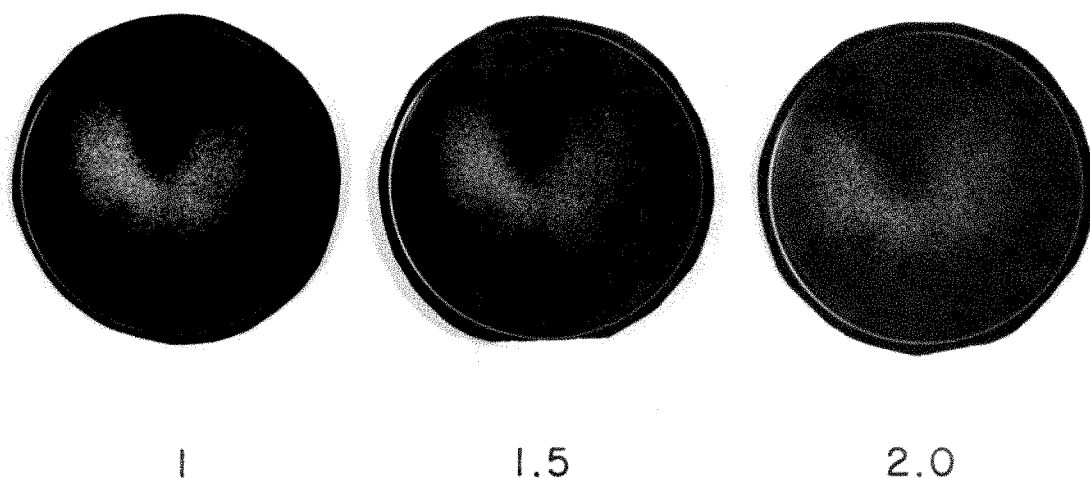


FIG. 5. Three gamma camera pictures of the same phantom setting are taken with 1, 1.5 and 2 imaging sizes. The resolution of the scans varies as the imaging size is changed. A better resolution is obtained with a 1.5 imaging size.

the frame and shows some distortion. Since there is very little difference between the size 1 and 1.5, we chose the larger size of 1.5 for the optimum imaging size in the thyroid study. If the thyroid gland is markedly enlarged, the imaging size of 1 may need to be used or the distance between the collimator and the neck increased. Figure 6 shows the imaging distortion due to off center

positioning and points out the necessity of properly placing the center of the thyroid gland at the center of the collimator. In Figure 7 the effect of defocusing or blurring of the dots is demonstrated. The resolution of various filling defects in the phantom is slightly increased by a $\frac{1}{3}$ defocusing of the dot. Resolution worsens as defocusing is increased.

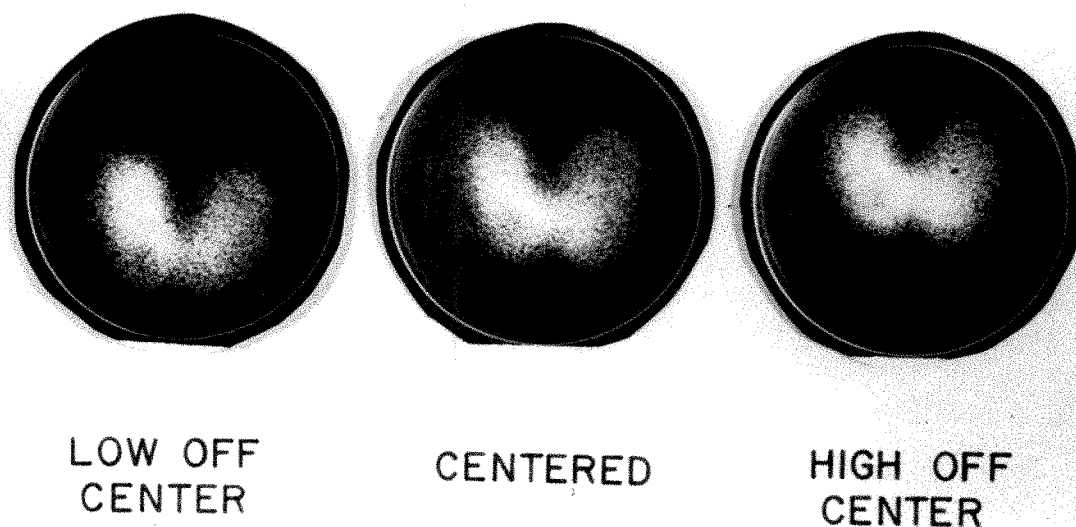


FIG. 6. Three gamma camera pictures of the same phantom setting are taken with a change in the position of the phantom to the pinhole collimator. A better resolution is obtained when the center of the phantom is set at the center of the pinhole collimator.



FIG. 7. Three gamma camera pictures of the same phantom settings are taken with 'defocusing' (blurring) of the image dots. *Left:* $\frac{1}{3}$ blur; *middle:* $\frac{2}{3}$ blur; *right:* maximum blur. A better resolution is obtained with only $\frac{1}{3}$ blur.

ILLUSTRATIVE CASES

CASE I. This 74 year old female experienced general weakness and weight loss since March 1965. She had noted an enlargement of the neck for about 2 years. Clinically, the diagnosis was hyperthyroidism. A nodule, 2 cm. in diameter, was palpable in the lower one-third of the left side of the neck. The T-3 uptake of the red blood cells was 24.6 per cent at the hyperthyroid range. The patient was given 82.8 μc of I^{131} for thyroid scanning. Figure 8, *A* and *B* shows the polaroid picture made with the scintillation camera and the photoscan ob-

tained with a mechanical scanner. The thyroid lobes are long and enlarged and are encroaching on the sternal notch. The palpable nodule is demonstrated in the lower one-half of the left lobe and shows hyperfunction compared to the surrounding thyroid tissue.

CASE II. This 58 year old female was admitted with abdominal pain, fever and headache. Admission physical examination revealed a large mass in the right neck. This was soft, well circumscribed and measured about 4.5 cm. in diameter. The patient had no thyroid symptoms. She was given 65.6 μc of I^{131} for thyroid

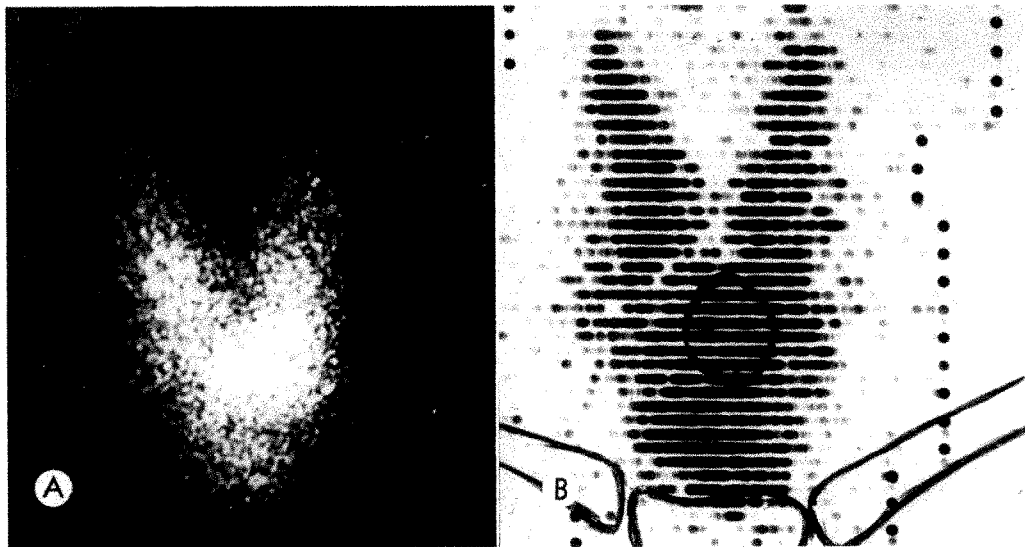


FIG. 8. (*A*) A gamma camera picture and (*B*) a photoscan of Case I showing the enlarged lobes with a hot nodule in the lower one-half of the left lobe.

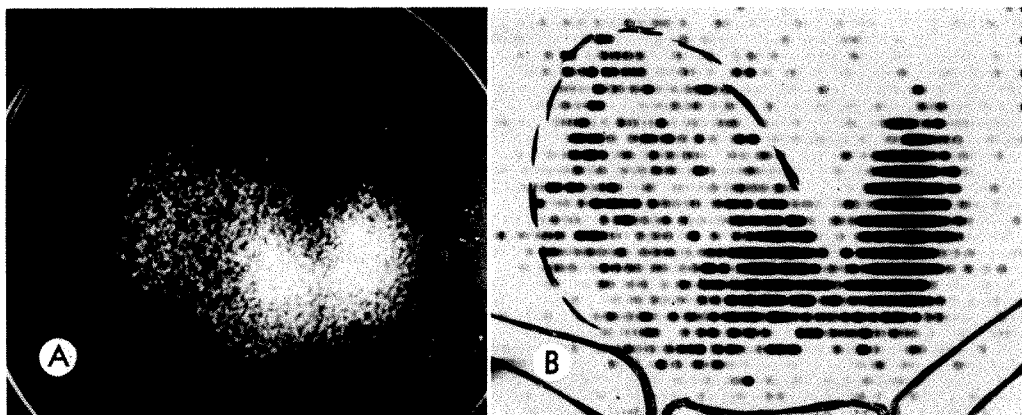


FIG. 9. (A) A gamma camera picture and (B) a photoscan of Case 11 showing a large area of decreased uptake in the latero-superior aspect of the right lobe. This proved to be a large adenoma. The entire thyroid gland is displaced to the left.

scanning. Both the scintillation camera picture and the photoscan (Fig. 9, A and B) showed the entire thyroid gland to be displaced to the left, due to a mass pressing on the supero-lateral aspect of the right lobe. The obviously cool mass originating from the right lobe was excised and proved to be an adenoma pathologically.

COMMENT AND CONCLUSION

Scanning time for a thyroid gland using a 3 by 2 inch crystal scanner usually takes about 12 to 16 minutes, provided there is an adequate count in the thyroid. Ordinarily, the oral tracer dose for thyroid scanning is in the range of 50 to 100 μ c of I^{131} . With the same amount of radioactivity and by using the scintillation camera, the scanning time is about 4 to 6 minutes. The real difference between these two systems of thyroid scanning is the time required and the location of an anatomic landmark. Although with the scintillation camera, the scanning time is less than half of that using a mechanical scanner, the mechanical scan gives a life sized picture with a clear anatomic land-

mark. As far as the actual resolution is concerned, there is probably very little difference between these two systems. We have been able to demonstrate a nodule as small as 1.5 to 2.0 cm. in diameter by either scanning system.

Department of Radiology
University of Pittsburgh
School of Medicine
Presbyterian-University Hospital
Pittsburgh, Pennsylvania 15213

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RADIONUCLIDE VENOGRAPHY USING TECHNETIUM ^{99m} PERTECHNETATE AND THE GAMMA-RAY SCINTILLATION CAMERA*

By LEONARD ROSENTHALL, M.D.
MONTREAL, QUEBEC, CANADA

THE advent of the gamma-ray scintillation camera has opened new vistas in nuclear medicine. Aside from reducing organ imaging time by a factor of 5 to 20 relative to conventional automatic scintillation scanners, it is also capable of dynamically visualizing major vessels when a large dose of a radioactive test agent is rapidly injected.^{4,5} We have been investigating the merits of the "radionuclide angiogram" and trying to determine its place relative to roentgen angiography. The results achieved with the major veins of the trunk and extremities and the technique used to produce these venograms are reported.

METHOD AND MATERIAL

The gamma-ray scintillation camera employed in this study was the Pho/Gamma manufactured by Nuclear-Chicago. The principles and method of operating this device have been fully detailed in the literature.¹

The test agent used was technetium ^{99m} pertechnetate in doses of 5 to 10 mc. The total body exposure is estimated to be 13 millirads per millicurie Tc^{99m} . The thyroid, stomach and large bowel receive about 270, 100 and 150 millirads, respectively.⁶

To visualize the superior vena cava, innominate, subclavian and axillary veins, a rapid injection of 5 to 10 mc of Tc^{99m} is made into an appropriate antecubital vein and serial imaging exposures of 5 seconds or less are obtained with the Polaroid camera or a programmed 35 mm. Robot* camera. When a good antecubital vein is not available, a 25 gauge needle and a superficial vein in the forearm or hand are used in as-

sociation with a "Velcro"† blood pressure cuff. The cuff is inflated to a pressure midway between systolic and diastolic for about 1 minute. It is then further inflated above systolic pressure, the Tc^{99m} is injected and then the cuff is rapidly released while still inflated.³

A superficial dorsal vein in the foot, a 25 gauge needle and a "Velcro" blood pressure cuff technique were used to obtain the radionuclide angiograms of the inferior vena cava, deep and superficial femoral, and iliac veins in all cases. The Tc^{99m} venograms were made with the patient supine and the detector head in contact with the anterior surface.

RESULTS

INFERIOR VENA CAVA

Serial scintiphotographs are shown in Figure 1 of a normal left common iliac vein and inferior vena cava following an 8 mc injection of Tc^{99m} into a superficial vein on the dorsum of the left foot. Note the appearance of the aorta to the left of the inferior vena cava in the 15–19 second exposure. The kidneys are demonstrated in the 20–24 second scintiphotograph.

Figure 2, *A* and *B* shows right and left common iliac Tc^{99m} venograms, respectively, of a patient with retroperitoneal fibrosis. Figure 2*C* is a contrast venogram, which shows narrowing and displacement of the inferior vena cava to the right. The Tc^{99m} venograms, which were obtained by separate injections of the right and left foot, accurately reflect the nature of the inferior vena cava involvement.

* Tektronix, Inc., Beaverton, Oregon, U.S.A.

† Available from the Taylor Instrument Company, Rochester, New York, U.S.A.

* Presented at the Annual Meeting of the Canadian Association of Radiologists, March 3, 1966, Montreal, Quebec, Canada. This work was supported by the John A. Hartford Foundation.

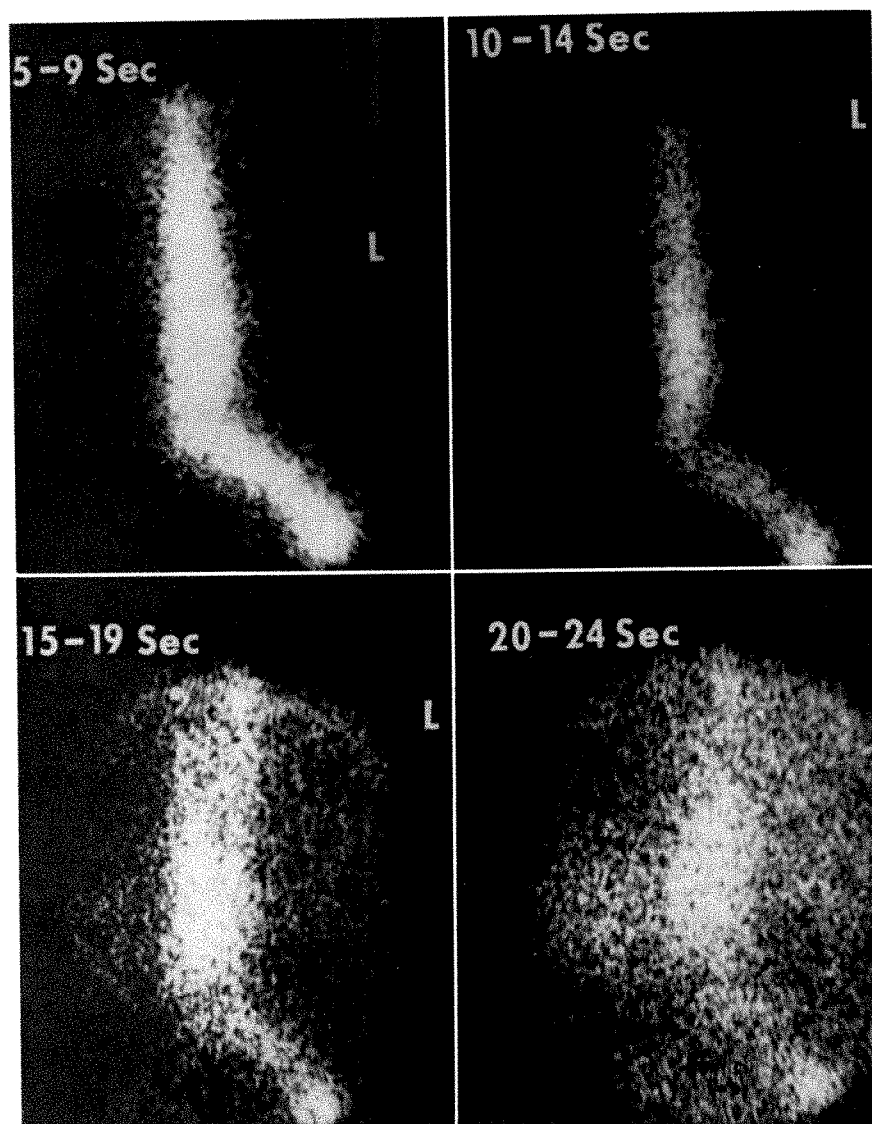


FIG. 1. Serial scintiphotos of the left common iliac vein and inferior vena cava following an injection of 8 mc of $\text{Te}^{99\text{m}}$ pertechnetate into a superficial vein on the dorsum of the left foot.

The venograms of a patient with left lower extremity edema, which developed 3 months following total cystectomy for carcinoma of the urinary vesicle, are shown in Figure 3, *A* and *B*. Obstruction of both common iliac veins is demonstrated, and, in addition, a collateral flow on the left is seen.

An obstructing thrombus of the inferior vena cava is demonstrated in Figure 4, *A* and *B*, which was taken over the lower and upper abdomen, respectively. The activity

is seen flowing out of the inferior vena cava in Figure 4*A* and in Figure 4*B* a wide band of paravertebral activity is superimposed on a higher than normal background. Although the detector head of the camera included the lower half of the heart, no activity is present in the right atrium as the blood was diverted to the superior vena cava, resulting in increased circulation time and dilution of activity beyond discrimination as a bolus.

Figure 5, *A*, *B*, and *C* shows scintipho-

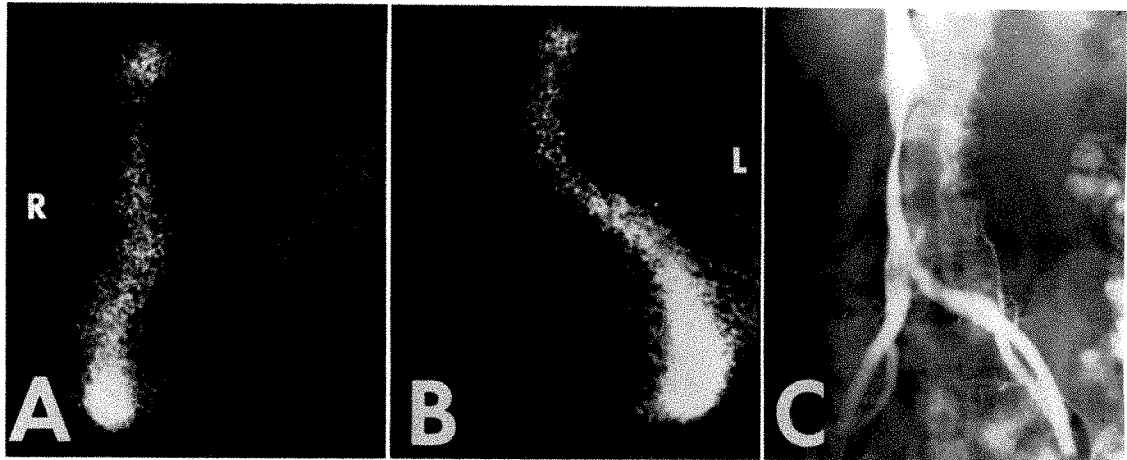


FIG. 2. (A) Right common iliac vein and inferior vena cava in a patient with retroperitoneal fibrosis. (B) Left common iliac vein and inferior vena cava of the patient in A. (C) Contrast inferior vena cavagram of the patient in B and C. Narrowing and displacement of the inferior vena cava were due to retroperitoneal fibrosis.

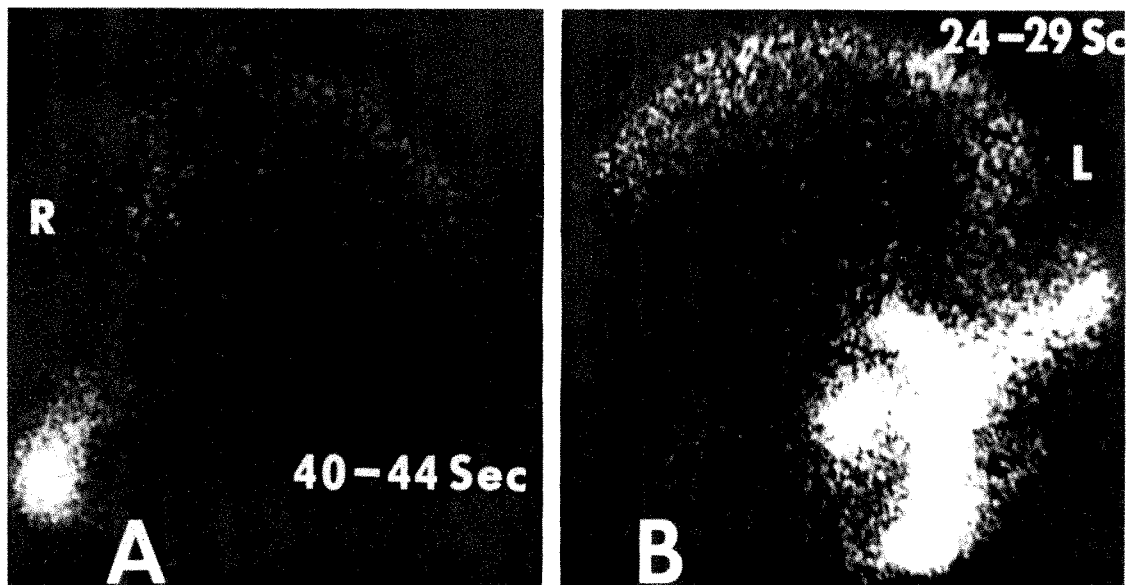


FIG. 3. (A) Tc^{99m} venogram of a patient with urinary bladder carcinoma infiltrating the pelvis. There is obstruction of the right common iliac vein. Scintiphograph made between 40 and 44 seconds post-injection. (B) Same patient as in A. Twenty-four to 29 second scintiphograph showing obstruction of the left common iliac vein with collateral circulation.

»»»»→

FIG. 5. (A, B and C) Zero to 4, 5 to 9 and 10 to 14 second scintiphographs, respectively, of the chest showing an occluded right innominate vein in a patient with a superior sulcus bronchogenic carcinoma.

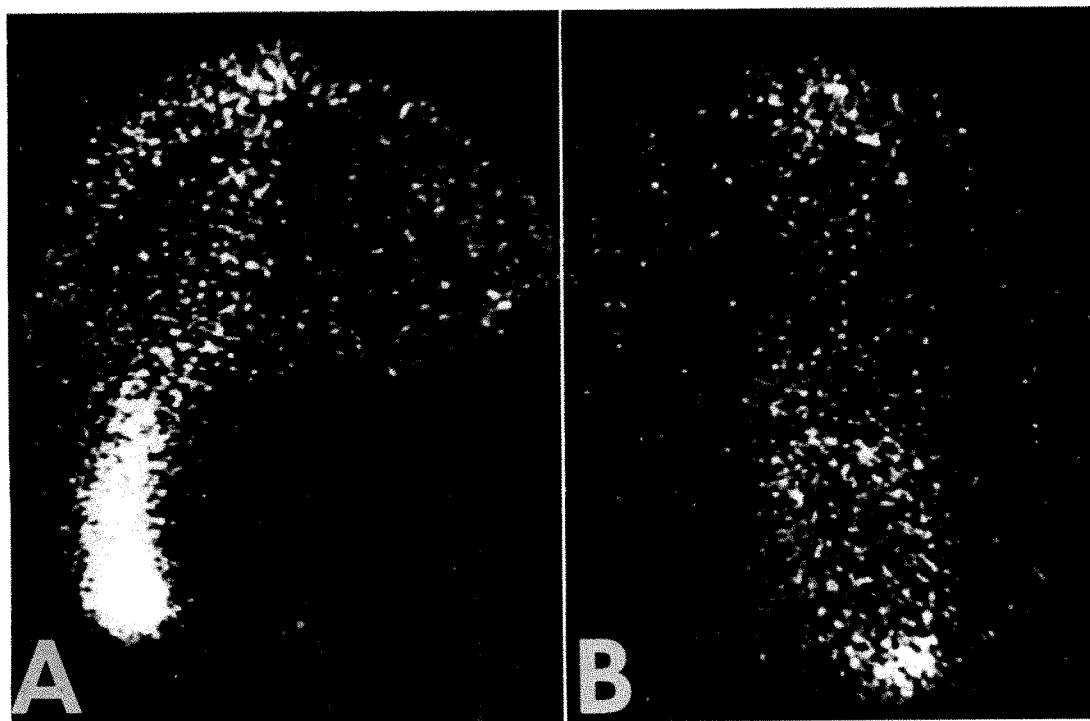
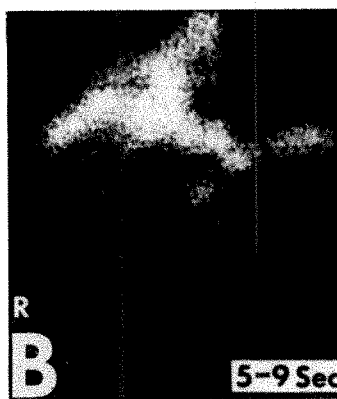
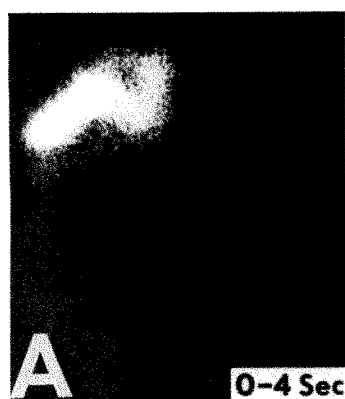
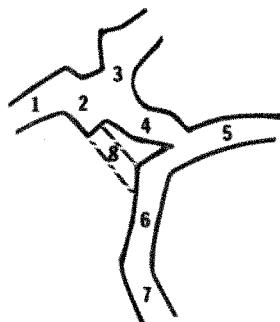


FIG. 4. (A) Tc^{99m} venogram obtained over the lower abdomen showing a normal right common iliac vein but with markedly reduced flow in the inferior vena cava associated with collateral flow laterally. (B) Same patient as in A, with the detector head over the upper abdomen. The inferior vena cava is not visualized, but there is a paravertebral flow directing the blood to the superior vena cava; hence, the poor visualization of the heart which is barely detectable at the upper border of the scintiphograph.



R



R

- 1 Axillary vein
- 2 Subclavian vein
- 3 Internal Jugular vein
- 4 Collateral vein
- 5 Left Innominate vein
- 6 Superior Vena Cava
- 7 Right heart
- 8 Occluded right Innominate vein

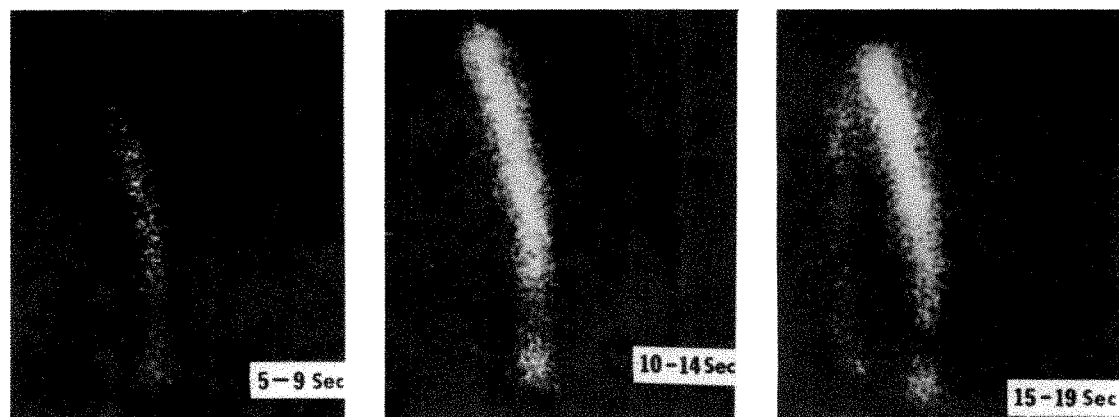


FIG. 6. Five to 9, 10 to 14 and 15 to 19 second scintiphotographs, respectively, of the left thigh demonstrating the deep and superficial femoral veins.

graphs, using Tc^{99m} , of a 52 year old male with a bronchogenic carcinoma of the right superior sulcus who presented with venous distention of the right arm and both jugulars. Note the early reflux into the right jugular vein from the subclavian vein in Figure 5A. In Figure 5B more activity is demonstrated in the neck and there is entry into the left innominate vein through collateral circulation, bypassing the occluded right innominate vein.

LOWER EXTREMITIES

Figure 6 is a series of 3 successive scintiphotographs of the left thigh, showing normal deep and superficial femoral veins. In Figure 7B, a radionuclide venogram, a varix of the deep femoral vein is demonstrated. Figure 7A is the corresponding contrast venogram.

DISCUSSION

It is apparent that the major veins can be readily visualized and their patency and displacement accurately determined. Professional time and patient exposure are reduced. Insofar as resolution is concerned, it falls considerably short relative to roentgenography. The radionuclide venogram, in the present state of apparatus design, is relegated to the role of a useful screening procedure.

The scintillation crystal is 11 inches in diameter, but the useful field is only about 9 inches. This restriction in field size makes

multiple injections necessary to define, for example, the entire inferior vena cava and common iliac veins. Large crystals are being developed to circumvent this limitation in part.

Multiple injections of Tc^{99m} , even with its physical half life of 6 hours, produce a progressively increasing background which tends to reduce delineation of the bolus. A shorter lived nuclide of the order of 2 to 10 minutes would be more desirable. Larger doses and shorter imaging times of the



FIG. 7. (A) Contrast venogram demonstrating a varix in the deep femoral vein. (B) Tc^{99m} venogram of the patient in A. Note the increased activity corresponding to the varix.

order of 0.1 second would then be possible. Bender and Blau² used $\text{Ba}^{137\text{m}}$ (2.6 minutes half life) to visualize the heart chambers, but the 660 kev. gamma emission poses problems in protection and collimation. The ideal radionuclide should have a half life between 2 and 10 minutes, a gamma energy in the range of 100 to 150 kev., no particle emission and derived from a long lived parent.

SUMMARY

The $\text{Tc}^{99\text{m}}$ venogram obtained with the gamma-ray scintillation camera is adequate to provide information on patency and gross displacement of the major vessels. It serves as a valuable, simple and quick screening procedure. The resolution of the radionuclide venogram does not compare favorably with the contrast venogram, but it can select patients for the more detailed roentgenographic procedure when necessary.

Illustrations of $\text{Tc}^{99\text{m}}$ venograms of the trunk and lower extremities are presented.

Department of Radiology
Montreal General Hospital
Montreal 25, Quebec, Canada

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SIMPLIFIED PREPARATION OF TECHNETIUM ^{99m} SULFIDE COLLOID FOR LIVER SCANNING

By DENNIS D. PATTON, M.D.,* EUGENE N. GARCIA, Ph.D.,† and MILO M. WEBBER, M.D.‡
LOS ANGELES, CALIFORNIA

THE recent introduction of technetium ^{99m} into the scanning field by Harper and others^{11,19} has been followed by a crescendo of interest in this remarkable isotope. Its chemical versatility suggests its use in a variety of chemical forms for selective uptake by different body organs. Technetium ^{99m} has been used for liver scanning in a fat emulsion¹² and in the form of a sulfide colloid.¹³ The method of preparation described by Harper involves the formation of insoluble colloidal technetium heptasulfide from sodium pertechnetate solution by the action of hydrogen sulfide gas. This method yields a mixture of colloidal and soluble technetium forms which, after the soluble forms are removed, is suitable for obtaining liver scans of high resolution and excellent counting statistics with a relatively low radiation dose.

The present authors wish to introduce a more simple, rapid, and efficient method of preparing the technetium sulfide colloid, a method which can be used by anyone having a Tc^{99m} generator and a few common items of equipment. The method involves the use of rhenium as a carrier for technetium, and the use of thiosulfate, rather than hydrogen sulfide, as a means of forming technetium sulfide colloid. It is hoped that a simpler method of preparation will encourage the more widespread use of technetium sulfide colloid for liver scanning.

MATERIALS AND METHODS

PREPARATION OF Tc_2S_7 COLLOID

Sterile Tc_2S_7 colloid can be prepared rapidly and conveniently as follows: Ten mc Tc^{99m} as TcO_4^- in saline is obtained from a Mo-99 cow, and is transferred through a

Millipore filter to a sterile 20 ml. rubber-stoppered injection vial. To this are added (all in sterile aqueous pyrogen-free solution) 10 mg. sodium thiosulfate ($Na_2S_2O_3$), 8 mg. gelatin, 2.5 mg. potassium perrhenate ($KReO_4$), and, finally, 1 ml. 1 *N* hydrochloric acid. The total volume of solution is about 15 ml. The mixture is placed in a boiling water bath immediately after the acid is added, and kept at 100° C. for 5 minutes; it is then cooled with running water. Four ml. 0.2 M phosphate buffer (pH 7) is added. Prepared in this way, the colloid mixture is a light brown opalescent suspension. The total preparation time is less than 10 minutes. Ten mc of Tc_2S_7 is enough for 3 liver scans.

Analysis for soluble TcO_4^- by dialysis of the colloid against normal saline for 2 hours shows that less than 2 per cent of the activity can be dialyzed out. The colloid as prepared is sufficiently sterile for intravenous administration. The reagents are prepared in bulk ahead of time, in autoclavable, multiple-dose, rubber-capped bottles, using pyrogen-free water. The reagent bottles are autoclaved and stored. For convenience, the thiosulfate, perrhenate, and gelatin may be combined into a stock solution.

COLLOID YIELD

The yield of the Tc_2S_7 colloid depends on (1) absence of soluble Tc forms and (2) absence of macroaggregates. That there was little soluble TcO_4^- remaining in the colloid mixture was shown by dialysis; less than 2 per cent of the total activity could be dialyzed out in 2 hours. The appearance of only trace amounts of activity in the urine provided further evidence, as did the

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* Department of Radiology, University of California, College of Medicine, Los Angeles, California.

† Department of Biochemistry, University of California, College of Medicine, Los Angeles, California.

‡ Department of Radiology, UCLA Center for the Health Sciences, Los Angeles, California.

absence of radioactivity in the kidney and bladder as shown on the scans. That there was no macroaggregate or noncolloidal precipitate was demonstrated by the lack of settling upon standing and by the absence of uptake in the lungs; had there been macroaggregates, intravenous injection would have yielded a lung scan. The combination of these results establishes the fact that this method of preparing Tc_2S_7 colloid gives an almost quantitative yield of stable colloidal material, free from both soluble activity and large particles.

CLINICAL RESULTS

The technetium 99m sulfide colloid preparation has been used in our department almost routinely for liver scans, with resolution and statistics greatly improved over that of the conventional Au^{198} scans, and with a lower radiation dose to the liver. No untoward reactions have occurred. Twenty minutes after intravenous administration of 3 mc of Tc_2S_7 colloid, scanning is done (on the Nuclear Chicago Pho-Dot Scanner) using the 19 hole collimator at a speed of 180 cm./min. (Higher scanning speeds would be quite justifiable.) Counting rates obtained have been in the 100,000 cpm range. The activity is taken up by the reticuloendothelial cells of the liver and, in some cases, also by the spleen. Kidneys,

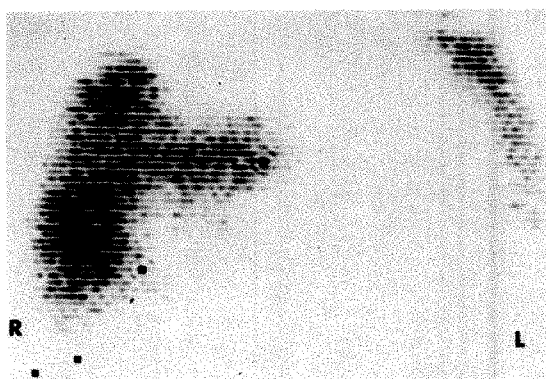


FIG. 1. Liver scan of patient with known liver metastases from carcinoma of stomach; scanning was done 20 minutes after intravenous injection of 3 mc technetium 99m sulfide colloid. Note the smooth gray scale, the improved definition, and the absence of extraneous background.

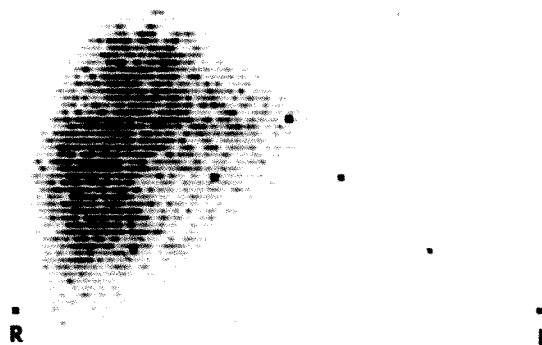


FIG. 2. Liver scan of same patient as in Figure 1, 20 minutes after intravenous injection of 200 μc colloidal Au^{198} . Note the irregular gray scale, the statistical fluctuations, the loss of definition, and the extraneous background; the nature and extent of the liver involvement might have been missed by this technique.

bladder, and lungs are not visualized. Statistics of the scan are excellent. Filling defects 1 cm. in diameter can be seen under favorable circumstances. It is interesting to note that 24 hours after the initial scan, a repeat liver scan can be done using the scanning speed usually employed in the conventional 200 μc Au^{198} liver scan, and yielding approximately the same counting statistics.

Figure 1 shows a liver scan of an 80 year old patient with liver metastases from carcinoma of the stomach; the scan was done 20 minutes after intravenous injection of 3 mc Tc_2S_7 colloid. The metastatic filling defects are clearly seen, and the high count rate (150,000 cpm) gives an image of smoothly varying shades of gray. A liver scan of the same patient was done 3 days later, using 200 μc of Au^{198} . This scan is shown in Figure 2. The maximum count rate in this scan was 22,000 cpm, and the inferior statistics gives rise to spurious fluctuations in density, the "salt-and-pepper" effect.

Monitoring the urine for 24 hours after intravenous injection of 3 mc Tc_2S_7 showed that less than 0.2 per cent was excreted via the kidneys. Monitoring of the liver showed that the effective half-life of the technetium 99m colloid is equal to its physical half-life of 6 hours; *i.e.*, it is retained indefinitely in



FIG. 3. Scan of 1,500 ml. phantom containing 200 μ c Au^{198} , with 2 "cold" lesions. The 4.5 cm. lesion is clearly visible; the 1.8 cm. lesion near the top is barely detectable. There is an apparent lesion at the lower right border. Note the statistical fluctuation of the count rate, causing a "salt-and-pepper" effect; also note the extraneous background due to scatter.

the liver. The radiation dose to the liver from Tc_2S_7 colloid is less than 1 rad per 3 mc scan dose²⁵ as compared to 10 rad per 200 μ c of Au^{198} .

Figure 3 shows a scan of a phantom containing 200 μ c of Au^{198} in 1,500 ml. of water, with two "cold" lesions of 4.5 cm. and 1.8 cm. diameter. Figure 4 shows a scan of the same phantom with 3 mc Tc^{99m} , using identical scanning parameters (90 cm./min., 20 per cent suppression).

Comparison of the 2 scans shows that in the Au^{198} scan (200 μ c) only the 4.5 cm. lesion is clearly seen; the 1.8 cm. lesion is detected but may possibly be missed due to the spottiness of the image. Other lesions may be read in, such as the irregularity at the lower right. Collimation failure for the relatively high energy photons caused an extraneous background in areas known to



FIG. 4. Scan of a 1,500 ml. phantom containing 3 mc of Tc^{99m} , with the same 2 "cold" lesions. There is better definition of the 4.5 cm. lesion and the 1.8 cm. lesion is well visualized. The borders of the phantom are seen to be intact. Note the greatly improved statistics and the absence of extraneous background.

be free from activity. With the Tc^{99m} scan (3 mc), the 4.5 cm. lesion is sharply delineated; its size, shape, and contour can be described. The 1.8 cm. lesion is unequivocal and can be described in terms of approximate size and shape. The background outside the phantom is negligible. The phantom image does not suffer from the degradation of respiration artifact and is, of course, sharper and clearer than the same lesion would be *in vivo*.

DISCUSSION

The formation of Tc_2S_7 in millicurie quantities involves such a minute amount of Tc^{99m} chemically that the Tc_2S_7 does not form a precipitate in the usual sense, even though the compound is very insoluble in water.^{1,6,10,11,16,26} There are roughly 10^{12} atoms of Tc^{99m} per millicurie, hardly enough to produce macroscopic chemical effects. Although 1 mc Tc_2S_7 prepared in aqueous medium may not precipitate by itself, it may form colloidal particles as a coprecipitate under favorable conditions, as will many sulfides, especially if prepared in the presence of a protective colloid such as gelatin.²⁰ Tc_2S_7 colloid hydrolyzes to soluble pertechnetate in aqueous medium, the hydrolysis being accelerated at extremes of pH.

In the original technique for preparing colloidal Tc_2S_7 ,^{11,13} hydrogen sulfide gas is bubbled through pertechnetate solution at pH 1, with gelatin added as protective colloid. The Tc_2S_7 appears as a colloid along with colloidal sulfur. Excess hydrogen sulfide is cleared from the solution by bubbling nitrogen gas through it. The neutralized solution is sterilized by filtration through a Millipore filter; but, because of the viscosity of the gelatin solution, filtration must be carried out under pressure. The procedure takes about 1 hour to complete, requires hydrogen sulfide and nitrogen gases, and must be carried out in a fume-exhaust hood; the technique requires apparatus not generally found outside research institutions. Using the recommended apparatus and procedures, the preparation

of the Tc_2S_7 colloid is not difficult, but the lack of this type of laboratory in ordinary radioisotope clinics that might wish to make use of Tc^{99m} colloid for liver scanning led the authors to investigate methods of preparation that could readily be carried out in an average clinic by personnel with average training. (Even with a fume-exhaust hood available, many nurses and technicians would be averse to working with hydrogen sulfide.) Our experience with preparation of colloidal Tc_2S_7 by the previous technique is that the colloid mixture usually contains considerable amounts of soluble Tc; the source of the soluble activity may be unconverted TcO_4^- , products of hydrolysis of Tc_2S_7 , or incomplete precipitation of Tc due to the presence of oxidation states other than +7, a condition that can occur in the presence of reducing agents, including hydrogen sulfide.^{1,16} The presence of soluble Tc is to be avoided in liver scanning because it will cause the kidneys to appear on the liver scan, and in man the right kidney generally cannot be distinguished from the liver in a combined scan. Hence, it is of considerable importance to ensure that the colloidal Tc_2S_7 is free from soluble Tc, and by the same token, free from macroaggregates containing Tc, as these would be trapped in lung capillaries and cause the lungs to appear on the liver scan. Several whole-body scans of the rabbit were performed by one of the authors using Tc_2S_7 prepared by the original method; all showed activity distributed in the salivary glands, thyroid, liver, spleen, stomach, kidneys, bladder, and bone. The colloid mixture can be freed from soluble Tc effectively by dialysis into a large volume of normal saline, or by passage through an anion exchange resin, but these procedures are inefficient and time consuming.

There are several methods by which Tc_2S_7 colloid might be protected from hydrolysis: (1) the use of protective colloids such as gelatin; (2) the use of a carrier isotope of technetium; and (3) the use of a carrier of some other element with similar chemical properties. Method 1 has been

used in previous preparations of Tc_2S_7 colloid^{11,13} and has been incorporated into the method employed by the present authors.

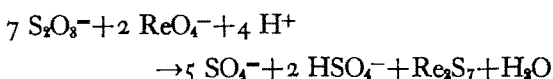
Method 2 might be feasible if Tc^{99} (half-life 2×10^5 yr.) were used as a carrier. The presence of relatively large amounts of Tc^{99} , also as Tc_2S_7 colloid, would retard the hydrolysis of the Tc^{99m} colloid by a factor equal to the ratio of the concentrations of the 2 isotopes. A protection factor of 10^6 would require 10^{18} atoms of Tc^{99} per mc of Tc^{99m} . This amount corresponds to 0.17 mg., or about $2.5 \mu\text{c}$ of Tc^{99} , about 10 per cent of the maximum permissible body burden;²² one would be reluctant to give this amount of such a long-lived radioisotope, especially as its elimination from the body is probably extremely slow.

Method 3 was investigated from the standpoint that rhenium, the heavier homologue of technetium, would have similar chemical properties.^{4,14,21} Group VII of the periodic table includes the halogens (F, Cl, Br, I, At) and three transition metals (manganese, technetium, and rhenium). The physiologic properties of all elements in Group VII show certain common trends.² Rhenium, the heavier homologue of technetium, was selected rather than manganese, the lighter homologue, on the basis of the principle that heavier homologue pairs have more similar chemical properties than lighter homologue pairs. Furthermore, manganese does not form a stable heptasulfide. A technique was devised for the coprecipitation of Tc_2S_7 and Re_2S_7 , the latter being in macroscopic quantity. Rhenium compounds have been used successfully in other applications to carry technetium.¹ For the present application, it was selected to use enough rhenium to give a protection factor of 10^6 ; this amounts to 0.32 mg. Re per mc Tc^{99m} . It is possible that this arbitrary factor is in excess of what is required for practical purposes and that adequate protection could be achieved by lesser amounts of rhenium. No indication was found in the literature that rhenium had been used as a carrier for Tc_2S_7 colloid, or that rhenium had been used in any clin-

ical application. Antimony sulfide has been used as a carrier for technetium sulfide,⁷ but the toxicity of antimony compounds would appear to make it less attractive than the more nontoxic rhenium.

With regard to the toxicity of rhenium, the literature offers evidence that rhenium is quite nontoxic. Animal studies show rhenium to be rapidly excreted from the body when in the soluble perrhenate form;^{3,15,17,18,24} its biologic half-life has been estimated to be 4 hours.⁵ No toxicity has been reported from the industrial use of rhenium,^{3,23} although generally less is known about the toxicity of expensive substances than common substances, as exposure is effectively minimized by economics. Maresh *et al.*¹⁸ found the L. D. for rats to be 900 mg. Re/kg. Hurd *et al.*¹⁶ gave 250 mg. potassium perrhenate IV to dogs, with no ill effects. The toxicity of a highly insoluble substance like Re_2S_7 is probably low on the basis of insolubility alone, and was referred to the toxicity of sulfides rather than rhenium.²³

In an effort to circumvent the need for hydrogen sulfide, preparation of the colloid was carried out using sodium thiosulfate to convert the pertechnetate to sulfide with gelatin added to stabilize the colloid. The reaction proceeds as follows (Tc being carried on Re):



This approach has been used in other applications.^{1,8,9} An alternate approach would be the use of thioacetamide;¹ sodium thiosulfate was selected on the basis of its low toxicity.²³ The colloid was prepared with gelatin as a protective colloid.

SUMMARY

Technetium 99m sulfide colloid can be prepared rapidly and conveniently by precipitation from pertechnetate eluted from a Tc^{99m} generator, using rhenium as a carrier, through the action of sodium thiosulfate. The use of presterilized reagents yields a sterile product, which is ready for

use without further processing. Gelatin is added as a protective colloid. No toxic materials or odoriferous gases are used. The product contains virtually no soluble technetium and no macroaggregates. Preparation time is less than 10 minutes, and can be done in a small area of any radioisotope clinic. Liver scans of high resolution and excellent counting statistics can be obtained with minimal patient radiation dose.

Dennis D. Patton, M.D.
Department of Radiology
University of California
College of Medicine
1721 Griffin Avenue
Los Angeles, California 90033

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TANDEM ELUTION OF TECHNETIUM 99m GENERATORS

By CARL R. BOGARDUS, JR., M.D., SEYMOUR H. LEVITT, M.D., and VERNON J. FICKEN, B.S.
OKLAHOMA CITY, OKLAHOMA

IN OUR institution we began using technetium 99 as the pertechnetate form ($\text{NaTc}^{99\text{m}}\text{O}_4$) for brain and thyroid scanning in March, 1965. We originally were able to use one 100 mc generator for 2 weeks; however, as the procedure became more widely accepted our load increased to the point where we found it necessary to order a new generator each week.

We use 20 ml. of sterile isotonic saline (pH 4.0) to elute the generator each morning. On the first day of milking a fresh 100 mc generator, the average output is found to be 77.8 mc. This, in 20 cc. of solution, was an acceptable concentration for administration. The dosage of $\text{Tc}^{99\text{m}}$ for brain scans is 8 mc intravenously. On Monday of the second week, however, the average output is 14.1 mc on the first day with subsequently less each following day. This is enough activity to do one scan but seldom more than this.

Thus it was necessary to have a fresh generator each Monday morning. We were then faced with the situation that (1) we either had to discard the old generator which still had considerable useful activity left or (2) we could milk both units and either use the eluates separately or combined. The second solution was our choice, since the additional activity was needed, especially when we began making and using technetium colloids and labeled albumin.

METHOD

The ideal solution consists of milking the two generators in tandem. The procedure is extremely simple, and the yield appears to be better than when they are milked separately. When the present tandem elution method is compared to separate elution, the yield is actually increased by 1 to 2 per cent.

Twenty cubic centimeters of sterile saline are used, as with the standard elution pro-

cedure, to milk the older generator first. The eluate from this unit is then allowed to run directly into the fresh generator and the final solution is collected from it. We have found that in addition to a slight increase in total output, we have a significant increase in the specific activity. The average Monday morning output of the two units in tandem is 93.1 mc in 20 cc. This is with a 1 week old generator of 16.5 mc of molybdenum 99 and a fresh generator of 100 mc of molybdenum 99.

Although it is possible to milk from the new unit into the old one, this decreases the amount of yield. Apparently, the high specific activity solution partially binds in the older generator, whereas the degree of binding in the reverse is insignificant.

In order to adequately shield and house the two generators in tandem and to minimize the amount of handling necessary, a special barn was constructed (Fig. 1). The barn was inexpensive in construction as the major portions were salvaged material. We used two lead 200 mc technetium generator shipping containers and turned the ends to an interlocking fit (Fig. 2). Lucite base inserts were turned on a lathe to hold the generators exactly centered within the lead shields. The two containers are identical so that at the beginning of each week the oldest generator is removed and discarded to decay and a new unit is placed in the shield. The relative position of the two shielded containers is then interchanged so that the older generator is always on top with the fresh unit below. The entire assembly is then closed with an interlocking lead cap on top and a Petrie dish below containing saline soaked gauze. The saline maintains the humidity within the barn at saturation at all times. This is necessary to prevent the resin from drying out.

In this manner, we are able to leave the

ends of the generators uncapped, which eliminates the necessity of constant daily exposure in removing and replacing the plastic end seal caps. Milking is easily accomplished by pouring the required amount of saline into the upper generator and replacing the lead cap. The Petrie dish is slid to one side and the eluate is allowed to drain directly into the syringe-filter assembly which is connected by a needle to a sterile collection bottle (Fig. 1).

After elution is completed, the Petrie dish is replaced to maintain the chamber humidity. A vacuum is applied to the collection bottle and the eluate is very promptly pulled through a .22 micron millipore filter and thereby sterilized. The entire procedure takes only a few minutes with minimal exposure and handling of the hot

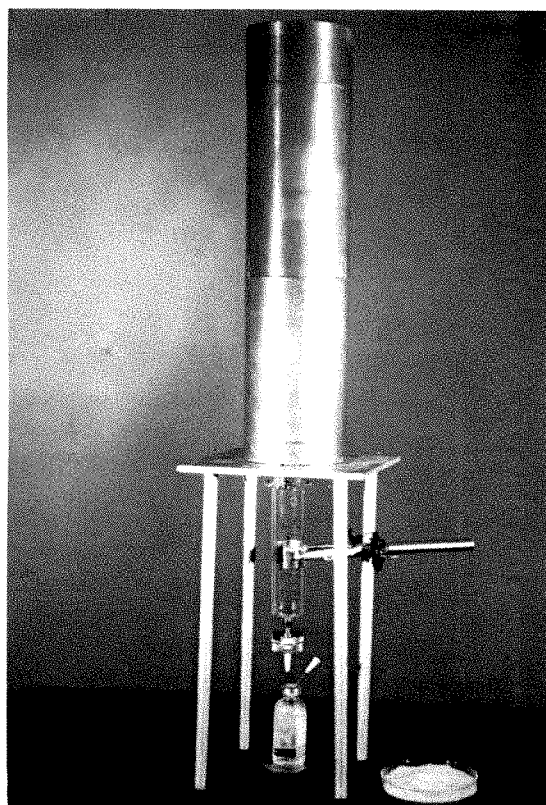


FIG. 1. Tandem generator assembly. Unit measures 70 cm. over-all height. Collection syringe, millipore filter and sterile bottle are shown assembled as they would be for elution. Saline Petrie dish is at the right of the unit.

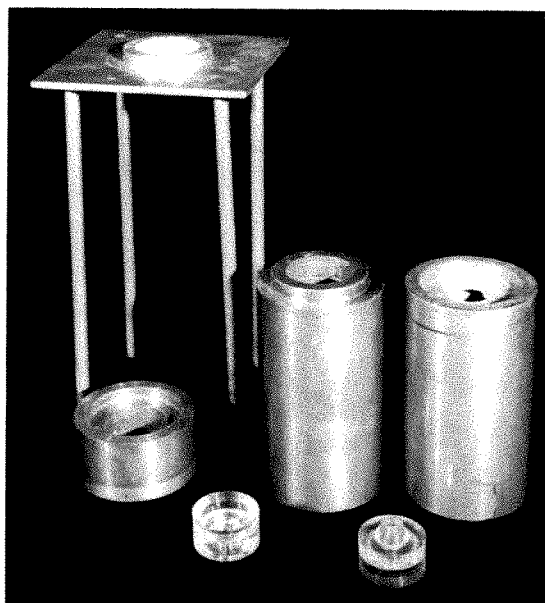


FIG. 2. Tandem generator assembly disassembled. Note the interlocking fit of the lead shields. The lucite inserts hold the technetium 99m generators exactly centered. Sharp cornered lips prevent unwanted running or dripping of the radioactive solution.

solution. Radiation exposure from a fresh non-eluted 100 mc generator under these conditions is 7.5 mr per hour at 25 cm. from the surface of the barn containing the generator. The same generator unshielded in air delivers 240 mr per hour at 25 cm.

SUMMARY

A simple method was devised whereby the elution efficiency could be increased by utilizing a fresh technetium generator coupled in tandem to the previous week's generator. A special barn was constructed so that the generators may be housed with a minimum amount of handling and be milked in tandem with ease.

Carl R. Bogardus, Jr., M.D.
Department of Radiology
The University of Oklahoma Medical Center
Oklahoma City, Oklahoma 73104

The authors wish to thank Mr. E. J. Davis, Chief Engineer of the Medical Center Physical Plant, for his technical assistance in the construction of the technetium 99 barn.

PRACTICAL MODIFICATIONS OF THE RECTILINEAR SCANNER*

By H. L. ATKINS

UPTON, LONG ISLAND, NEW YORK

SOME inadequacies in the commercial scanner used in our laboratory became apparent while investigating the use of Tc^{99m} in clinical studies. It was not possible to exploit the full potential of this nuclide with the existing apparatus. The high count rates should permit rapid scanning, and high resolution is theoretically possible with the efficient collimation designed for the relatively low energy gamma emission.

The density range of the photoscan produced by this equipment is intimately tied in with the rate meter scale and the contrast enhancement circuitry. Not only does the photorecording cathode-ray tube emit one pulse of light for each gamma ray detected, but the brightness of each light pulse is determined by the count rate at that moment. High count rates increase the voltage across the tube to a degree determined by a control (counts per minute range differential) relating this voltage to the per cent of full scale reading on the rate meter. Since the shortest time constant of the rate meter is $\frac{1}{8}$ second, this results in a considerable lag in photorecording tube response at high scanning speeds. For instance, at a speed of 60 cm. per minute, the detector will have moved more than 3 mm. in the time it takes for the photorecording tube voltage to achieve 90 per cent of the maximum difference across a transition zone in the scan. This results in a readily visible "scalloping" effect with each traverse over the "hot" area and degrades resolution considerably (Fig. 1).

A second limitation is in the indexing or line spacing. The usual collimators for the light emitted from the photorecording tube are 3 or 6 mm. in diameter which limits the maximum number of lines per centimeter. This makes it difficult to delineate regions

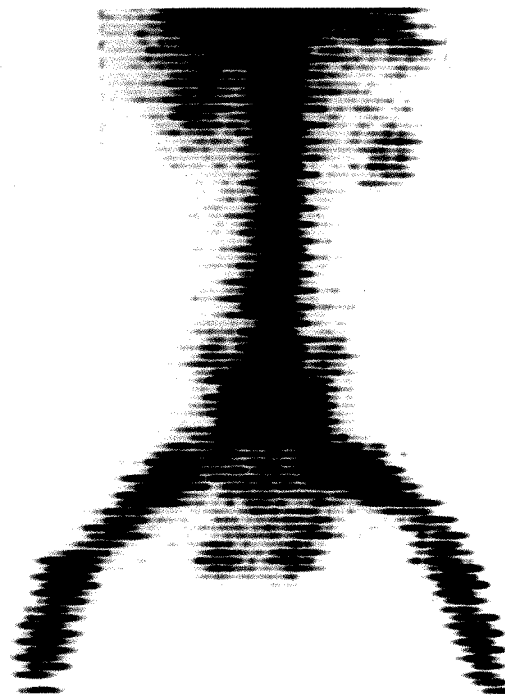


FIG. 1. Scan of rabbit bone marrow performed with technetium colloid. Maximum count rate was 4,500 per minute. Scanning speed was 30 cm. per minute with range differential setting of 40 per cent on the 10 K scale with a time constant of $\frac{1}{4}$ sec. Note extreme degree of "scalloping."

smaller than this on the scan, particularly in a direction perpendicular to the direction of the traverse of the detector. When smaller light spots are used, the scanning speed must be kept constant in order to maintain the statistical reliability of the data even though more lines per centimeter are used. This appreciably increases scan time.

In addition to the above limitations, the use of contrast enhancement or background erase prior to obtaining the data has been found to result in loss of information. If good statistical data are available, the film

* From the Medical Research Center, Brookhaven National Laboratory, Upton, Long Island, New York. Research supported by the U. S. Atomic Energy Commission.

response should show up meaningful differences in concentration of activity over the area scanned in an unambiguous manner. Should contrast enhancement be desired, it is best to perform such manipulations after the data are secured rather than run the risk of not recording areas of relatively low activity.

The teledeltos recording system is inadequate for recording high count rates at rapid scanning speeds. The dots fade out at about 800 per minute or higher. At a rate somewhere between 1,000 and 1,200 per minute, every other dot appears (Fig. 2). Therefore, the dot scan is poorly recorded at speeds above 66 cm. per minute when an optimum dot density of 12 per centimeter is desired.

These limitations have been emphasized with the use of Tc^{99m} . Collimators designed for 140 kev. gamma emission have combined high resolution with great sensitivity, and the low radiation dose permits the administration of millicurie levels of activity, sufficient for obtaining excellent statistical data. Count rates over 100,000 per minute are often achieved.

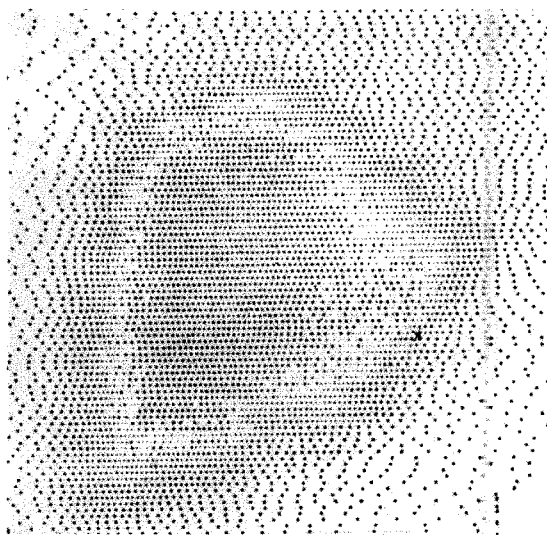


FIG. 2. Teledeltos recording of liver scan. Maximum count rate 260,000 per minute; scan speed 120 cm. per minute; dot factor 256. An apparent isocontour mapping is produced by fading out of the dots at count rates over 200,000 per minute and then recording of every other dot at still higher count rates.



FIG. 3. Normal thyroid scan with Tc^{99m} as pertechnetate. Note high background activity.

Another factor specific in the use of Tc^{99m} is the fact that usually less than 3 per cent is concentrated in the thyroid and fairly high background levels of activity are encountered in scanning this organ (Fig. 3). This rather large incidence of random density increase on the film can be a psychologic hindrance to accurate interpretation of the photoscan. The raster effect can also be bothersome, particularly if line spacing is not carefully adjusted.

With these factors in mind and with knowledge of the work performed at Argonne Cancer Research Hospital¹ and by Christie *et al.*² in Cleveland, we decided to modify our scanner in a number of ways in order to improve the system of data presentation.

DESCRIPTION OF EQUIPMENT AND MODIFICATIONS EMPLOYED

Our equipment is one in the early Picker Magnascanner series. It was obtained in February, 1961 and is not transistorized. The detector contains a 3×2 inch NaI (Th) crystal. The speed range was 0-60 cm. per minute and the indexing control was variable from a line spacing of 0.2 cm. to 1.0 cm.

The manufacturer instituted changes so that the scanning speed was doubled and now is continuously variable from 18 to 120 cm. per minute. At the same time, the line

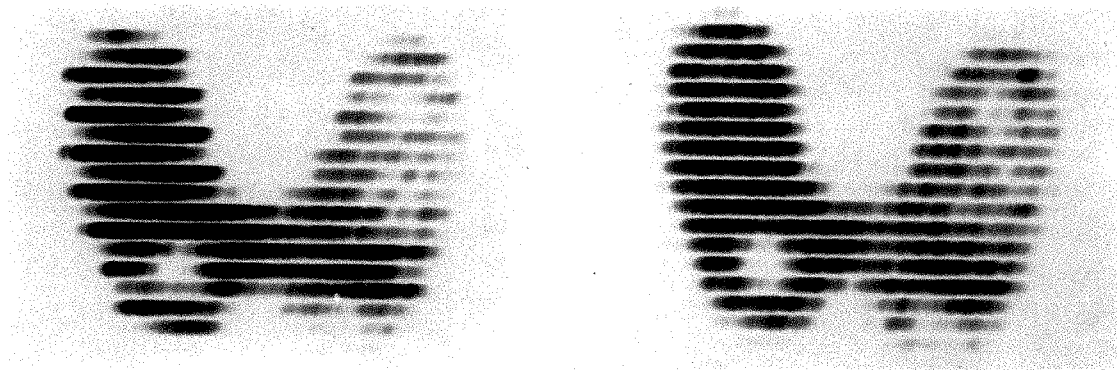


FIG. 4. Scans of thyroid phantom. Scan on the left was performed with contrast enhancement circuit intact. Speed 104 cm. per minute; maximum counts per minute 55,000; range differential 50 per cent on the 100 K scale with a time constant of $\frac{1}{8}$ sec. The scan on the right was performed at the same scanning speed but without contrast enhancement. The "cold" area in the left lower pole is due to absorption by the loading screw.

spacing adjustment was reduced by one-half so that it now can be varied from 0.1 to 0.5 cm.

All other modifications have been installed by ourselves. An on-off switch was inserted so that the signal from the rate meter to the photorecording circuit could be interrupted. This means no fluctuation of the photorecording tube voltage will occur with count rate changes. Actually, this same result can be obtained by placing the contrast control (counts per minute range differential) on 100 per cent, which means minimum contrast, and placing the rate meter scale on maximum (300,000 cpm full scale). If the maximum count rate is less than about 30,000 per minute, negligible voltage change will occur.

With this modification and a constant photorecording tube voltage, the density on the photoscan due to any level of activity is determined by density setting on the scanner (pulse duration in microseconds) and by scan speed. For each photon detected in the detector crystal, one pulse of light is emitted from the photorecording tube. The summation of pulses results in a density range on the film corresponding to 2.5 for areas of maximum activity to 0.2 for background when the photo recording tube voltage and density are set at a level predetermined by calibration scans. The only variable to be determined is scan speed.

This is a function of maximum count rate and thus the statistical data will be more or less constant from one scan to the next.

An example of the effect of this modification, which bypasses the contrast enhancement circuitry, is shown in Figure 4. The standard Picker thyroid phantom has been used. The right lobe contains twice the volume of the left lobe and a "hot spot" equivalent to the count rate over the right lobe is present in the left lower pole. "Cold" nodules measuring 5 mm. in diameter in the right upper pole, 12 mm. in the right lower pole, and 8 mm. in the left upper pole are also present. The scan on the left was performed in the conventional manner recommended by the manufacturer for minimal contrast enhancement. The maximum count rate was 55,000 per minute and the

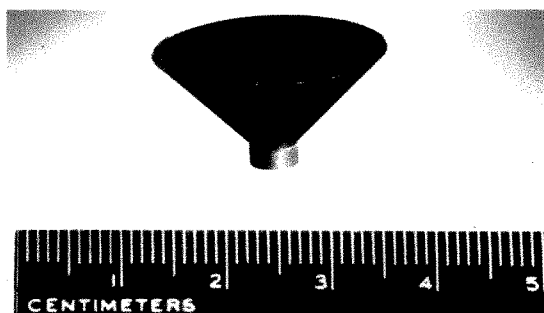


FIG. 5. Lucite collimator used to diffuse the light spot for photorecording. A gaussian filter is affixed to the top surface.

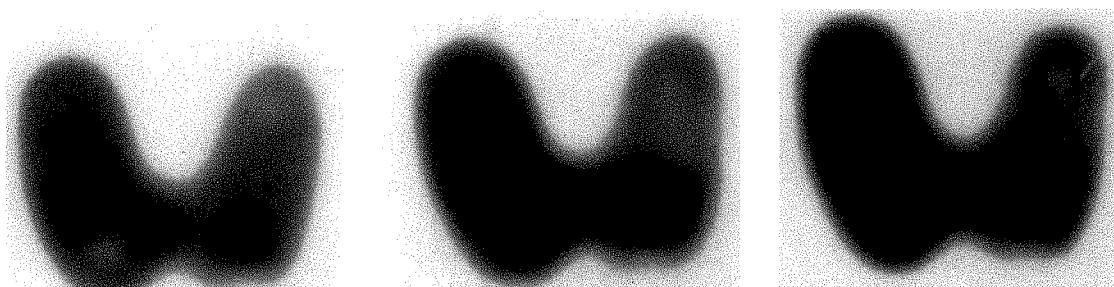


FIG. 6. Scans made with the data blending technique of thyroid phantom. No raster effect is seen with line spacings of 0.15 cm. (left), 0.2 cm. (middle), and 0.3 cm. (right). The smallest cold nodule is not well demonstrated photographically but can be seen in the original scan.

scan speed 104 cm./min. Line spacing is 0.35 cm. The irregular border of the thyroid due to scalloping is readily observed.

The right-hand scan was performed with the same scan speed but the contrast enhancement circuitry was bypassed. No scalloping is observed. In addition, a truer relationship of density representing the left lobe activity relative to the density over the right lobe is seen.

The next modification was modeled after the "data-blending" technique described by others. Following several attempts, the following system was adopted:

The support for the light collimator on the photorecording tube was shortened by $\frac{1}{4}$ inch. A collimator in the form of a lucite light pipe was constructed, as shown in Figure 5. It is an inverted cone measuring 22 mm. in widest diameter, tapering down to a stem 4 mm. in diameter and is 8 mm. long. The stem is made as short as possible (about 2 mm.) but long enough to be securely stable in the collimator support. Both upper and lower surfaces are etched with sandpaper in order to diffuse the light. The other surfaces are coated with aluminum paint.

This collimator produces a "blob" of light on the film, of greatest intensity in the center and fading toward the edges. When scans are made with this collimator, no raster effect is seen with a line spacing of 0.2 cm. or less, but is seen at wider spacings. A filter was then constructed to produce a light spot more gaussian in its distribution.

Two methods have been used to produce

filters. First, a series of circles were cut out of x-ray film of density 0.2 with diameters corresponding to t values for equal increments along the ordinate of the standard probability curve in the Handbook of Physics and Chemistry. These can be superimposed and then photographically reversed and reduced to the proper size. The diameter of the filter at the 50 per cent intensity level should be equivalent to the resolution of the detector collimator.

An alternate method is to cut out equal thicknesses of aluminum with, again, the diameter of the piece corresponding to 50 per cent of maximum height equal to the diameter of the 50 per cent isoresponse level of the detector collimator at focus, and the remaining pieces related to this according to the probability curve. This construction can then be x-rayed and the resultant image used as the filter.

With these filters, satisfactory light spots are produced which on photoscans show no raster effect at spacings 0.15 cm., 0.2 cm. or 0.3 cm. (Fig. 6). These are the indexing steps ordinarily used in this laboratory. Two light collimators are now available. One, which is our standard, produces a light spot approximately 1.2 cm. in diameter at the 50 per cent level; the other is 0.75 cm. in diameter.

SCANNING METHOD EMPLOYED

The densities on the photoscan represent contributions from above, below and to either side of any given point. The degree of contribution or the area over which the

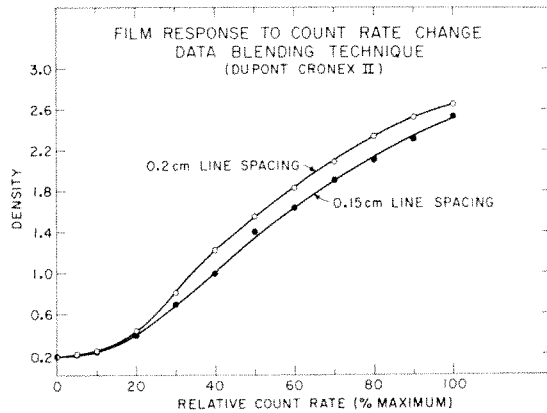


FIG. 7. Density on photoscan *versus* count rate. On this plot the points for the 0.15 line spacing curve were performed with a different filter. By adjusting photorecording tube voltage, the two curves could be made to coincide.

counts recorded are integrated depends on the size of the light spot. In the technique as described by Christie *et al.*² integration is over the area of 1 square inch. In the system being described, with a smaller light spot, the integration is more nearly over the area of a square centimeter, and calculations are based on this. Basically, in order to obtain satisfactory data, we have sought to have 1,800 counts per square centimeter. Therefore, scanning speed can be calculated by

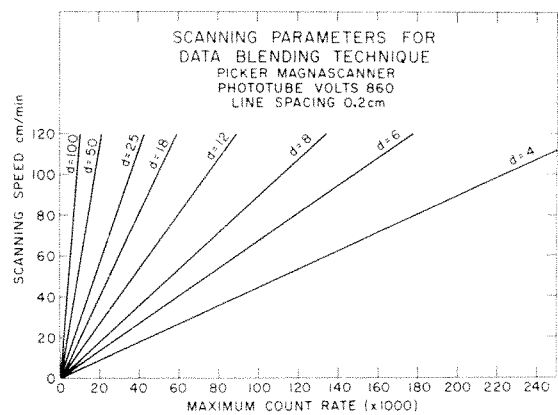


FIG. 8. Chart used to determine scan speed for the maximum count rate obtained over area of interest. Where time permits, the slower scanning speeds at the lower density settings are selected in order to provide greater statistical reliability and less "mottle."

the following formula:

$$\frac{\text{maximum counts/minute}}{1,800 \text{ counts/cm}^2} \times \text{lines/cm.} = \text{speed in cm./min.}$$

With our standard light collimator, a photorecording tube voltage of 860 at a density setting of 25 $\mu\text{sec.}$ gives the proper range of densities when this formula is used

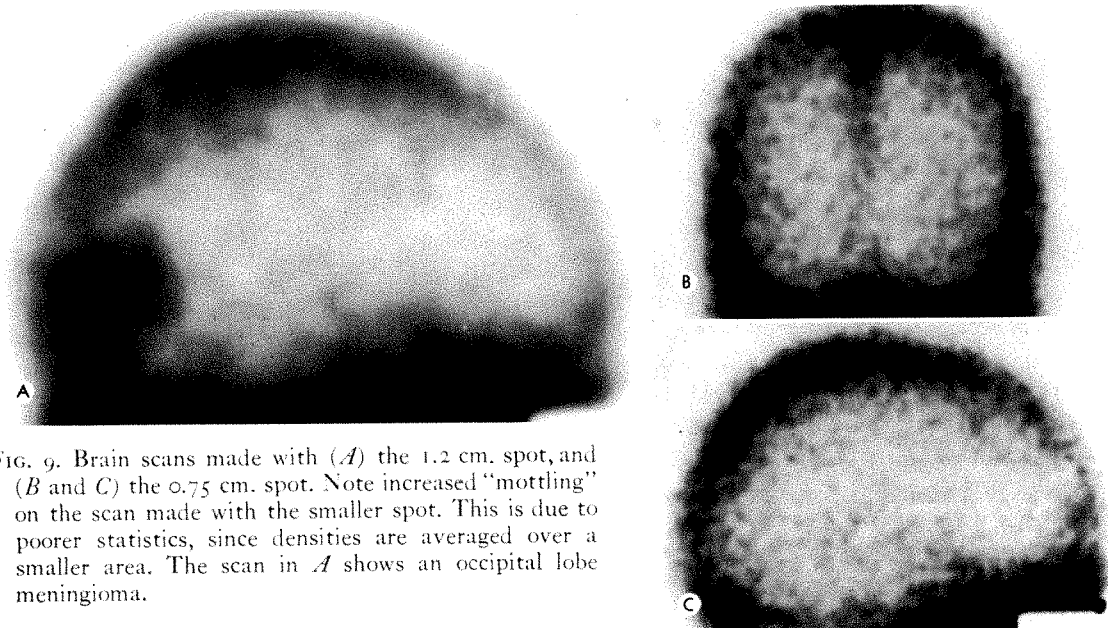


FIG. 9. Brain scans made with (A) the 1.2 cm. spot, and (B and C) the 0.75 cm. spot. Note increased "mottling" on the scan made with the smaller spot. This is due to poorer statistics, since densities are averaged over a smaller area. The scan in A shows an occipital lobe meningioma.

TABLE I

RESULTS OF 24 HR. I^{131} UPTAKE, PBI^{131} CONVERSION RATIO AND SALIVARY I^{131} /PLASMA PBI^{131} RATIO
ACCORDING TO CLINICAL GROUPS IN 1,086 PATIENTS
(Per cent of cases in parentheses)

Test	Euthyroid Group (664 Patients)			Hyperthyroid Group (319 Patients)			Hypothyroid Group (103 Patients)		
	Normal	Hyper- thyroid	Hypo- thyroid	Hyper- thyroid	Hypo- thyroid	Normal	Hypo- thyroid	Hyper- thyroid	Normal
Uptake	532 (80.0)	35 (5.2)	97 (14.8)	156 (49.2)	10 (3.1)	153 (47.7)	52 (50.0)	1 (0.9)	50 (49.1)
Conversion ratio	543 (81.7)	39 (6.0)	82 (12.3)	212 (66.4)	4 (1.2)	103 (32.4)	58 (56.3)	2 (1.9)	43 (41.8)
Salivary I^{131} /plasma PBI^{131}	525 (79.0)	71 (10.7)	68 (10.3)	141 (44.2)	14 (4.3)	164 (51.5)	53 (51.5)	1 (0.9)	49 (47.6)

until a fine particulate suspension is acquired

7. Allow to sit for at least 5 minutes, centrifuge, pour off clear supernatant fluid

8. Refill with TCA, resuspend precipitate, centrifuge again

9. Pour off supernatant, pick up excess TCA from inside tube with filter paper

10. Add 10 per cent NaOH to crayon mark restoring original volume, stir to dissolve precipitate

11. Place in well counter, obtain counts per minute

12. Conversion ratio

$$(\text{per cent}) = \frac{\text{NaOH count—background count}}{\text{Plasma count—background count}} \times 100$$

The samples of plasma or serum were counted in a scintillation well detector system. The crystal was a 2 by 2 inch sodium iodide (TI) and spectrometer scaler system. A minimum of 5,000 counts was obtained per sample.

The 24 hour salivary I^{131} /plasma PBI^{131} ratio was calculated as:

$$\frac{\text{net saliva count}}{\text{net } PBI^{131} (\text{NaOH count—background count})}$$

Our normal values have been derived by selecting 62 nonhospitalized patients in good physical condition with no apparent symptoms of thyroid disease. Of these cases, 58 were considered euthyroid, as determined by both clinical and routine

chemical methods. Of the remaining 4, 2 were found to be hyperthyroid and 2, hypothyroid, by the same criteria. Euthyroidal ranges were thus obtained as follows:

24 hour thyroid uptake—20–50 per cent

24 hour PBI^{131} conversion ratio—15–50 per cent

24 hour salivary I^{131} /plasma PBI^{131} ratio—2–60

RESULTS AND COMMENTS

In the euthyroid patients (Table 1), the individual per cent correspondence of the 3 tests to the clinical picture is relatively high. However, these percentages decline substantially in the hyperthyroid and hypothyroid groups. It is in these groups that the laboratory values are of critical importance. The percentages of normal values in these 2 groups are significant. It is unwise to discard the clinical impression of thyroidal alteration on the strength of one test alone. If, instead, a combined evaluation of the 3 tests is made and if the values of all or of 2 of the 3 studies correspond, then the clinically suspected thyroidal alteration may be confirmed or ruled out with greater ease. This evaluation takes also into account the borderline ranges of each of these tests and clarifies them in accordance with the values obtained in the others. In addition, thyroid disorders in clinically silent cases have been discovered, using this method of inclusive estimation. The cases in which 2 out of the 3 studies agreed were re-evaluated clinically as well as by means of repeat laboratory tests. The clinical evaluation took into account

TABLE II

COMBINED COMPARISON OF 24 HR. I^{131} UPTAKE, PBI^{131} CONVERSION RATIO AND SALIVARY I^{131} /PLASMA PBI^{131} TO THE CLINICAL STATUS

(Per cent of cases in parentheses)

Test	Euthyroid Group			Hyperthyroid Group			Hypothyroid Group		
	Normal	Hyperthyroid	Hypothyroid	Hyperthyroid	Hypothyroid	Normal	Hypothyroid	Hyperthyroid	Normal
All 3 agree	417 (62.8)	2 (1.2)	8 (1.2)	102 (32.0)	0 (0.0)	61 (19.4)	24 (23.3)	0 (0.0)	19 (18.4)
2 out of 3 agree	193 (29.2)	7 (1.0)	20 (3.0)	65 (19.8)	0 (0.0)	70 (21.6)	33 (31.9)	0 (0.0)	23 (22.2)
Total	610 (92.0)	9 (1.3)	28 (4.2)	167 (51.8)	0 (0.0)	131 (41.0)	57 (55.2)	0 (0.0)	42 (40.6)

changes obtained after therapeutic trials. The other methods of investigation included cholesterol and chemical PBI determinations as well as a wide range of I^{131} procedures. It was found that the diagnostic assumption, made on the basis of the correlation of 2 out of the 3 values under scrutiny, was valid in about 95 per cent of the cases.

In our series of 664 clinically euthyroid patients (Table II), 610 cases (92 per cent) can be classified by means of the combined evaluation of the 3 I^{131} tracer studies as normal. Of the remaining 54 cases, there were 2 patients with hyperthyroidal values and 8 patients with hypothyroidal values in all of the 3 studies. Further investigation, using other techniques, supported these conclusions. Twenty-seven patients had abnormal values for 2 of the 3 tracer studies, raising the suspicion of thyroid disease in the absence of symptoms or clinical findings. Finally, 17 patients had such marked discrepancies in the results of the 3 tracer studies that no conclusions could be reached. For example, one test was within the eu- or hyperthyroidal range while the other was at hypothyroidal levels.

Of the 319 patients judged to be clinically in the hyperthyroid group, using the same criteria of evaluation, 167 (51.8 per cent) disclosed hyperthyroidal values. In 131 (41 per cent), with clinical suspicion of hyperthyroidism, uniformly normal tracer values were found. No diagnostic conclusions were obtained in 21 cases due to discrepancies in the results.

Of the 103 patients classified as hypothyroid clinically, in 57 (55.2 per cent), the tracer studies confirmed the clinical impression, in 42 (40.6 per cent), the diagnostic procedures with I^{131} were normal, denying the suspected dysfunction and in 4 cases, the presence of discrepancies precluded the diagnosis.

A part of our study dealt with the evaluation of the salivary I^{131} /plasma PBI^{131} ratio as a diagnostic means of estimating thyroidal alterations. Observations of Thode and associates,^{22,23} and others, have shown the value of the salivary counts and salivary I^{131} /plasma PBI^{131} ratio as an aid in the diagnosis of thyroid dysfunction. On the other hand, Freinkel and Ingbar⁸ followed by Fellingner and collaborators⁷ have expressed doubts as to the presence of a specific relationship between the concentration of salivary iodine and the thyroid function. According to these authors, the salivary iodine merely reflects secretion of circulating iodide in an unchanged form and, as such, may be affected by other conditions besides thyroid dysfunction, mainly congestive heart failure and impaired renal function. In these diseases, a prolonged elevation of the plasma iodide causes high salivary counts as seen in myxedema.

Eliminating the 42 cases in which discrepancies were found, 1,044 patients were considered in the evaluation of the salivary I^{131} /plasma PBI^{131} ratio (Table III). Of these patients, 957 (91.6 per cent) had salivary I^{131} /plasma PBI^{131} ratios which were

TABLE III

SALIVARY I^{131} /PLASMA PBI^{131} RATIO IN 1,044 PATIENTS COLLATED WITH 24 HR. THYROID UPTAKE AND 24 HR. CONVERSION RATIO IN NORMAL AND ABNORMAL THYROIDAL CONDITIONS

(Per cent of cases in parentheses)

	Euthyroid Group	Hyperthyroid Group	Hypothyroid Group	
Salivary I^{131} /plasma PBI^{131} ratio	(647 Patients)	(298 Patients)	(99 Patients)	
Agrees with the other two tests	406 (62.1)	164 (55.0)	43 (43.4)	
Agrees with uptake alone	70 (10.8)	69 (23.1)	9 (9.0)	
Agrees with conversion ratio alone	122 (18.8)	40 (13.4)	34 (34.4)	
Total	598 (92.2)	273 (91.5)	86 (86.8)	957 (91.6)
Disagrees with the other two tests	49 (7.7)	25 (8.5)	13 (13.2)	

in agreement with the final diagnostic conclusions. Our series shows also that the lack of correlation between the salivary I^{131} /plasma PBI^{131} ratio and the other 2 tests was no greater than the disagreement of each one of the other 2 determinations with the other. Aside from attempting to relate, physiologically, salivary activity to thyroid function, our results show clearly that the salivary I^{131} /plasma PBI^{131} ratio has definite merit as an indirect method in the detection of thyroid disorders. This is mainly true if this determination is used in conjunction with the others.

A definitive diagnosis of thyroid disease is often very difficult and the laboratory work plays an essential role. Our investigation suggests that no single test is always sufficient, but a selected number of tracer studies can furnish results with a greater degree of accuracy.

CONCLUSIONS

The results of 24 hour I^{131} uptake, 24 hour PBI^{131} conversion ratio, and salivary I^{131} /plasma PBI^{131} ratio in 1,086 patients are analyzed.

A very high percentage of correlation (above 90 per cent) between the real clinical status and these tests can be obtained if comprehensive interpretation of their values is carried out.

The salivary I^{131} /plasma PBI^{131} ratio is established as a useful indirect index of thyroid activity.

Anthony A. Maglione, M.D.
Phelps Memorial Hospital
North Tarrytown, New York

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A COMPUTER PROGRAM FOR DIAGNOSIS OF THYROID DISEASE*

By LAWRENCE T. FITZGERALD, M.S., JOHN E. OVERALL, Ph.D., and CLYDE M. WILLIAMS, M.D., Ph.D.

GAINESVILLE, FLORIDA, AND GALVESTON, TEXAS

SINCE 1959, a computer program for the diagnosis of thyroid disease has been used on more than 1,300 cases of suspected thyroid disease in which adequate follow-up information was available to check its accuracy. An analysis of our diagnostic errors has led to major modifications of the program which have improved its usefulness. The purpose of the authors is (1) to describe the evolution of our program, and (2) to summarize the new features of our current program.²

EVOLUTION OF THE PROGRAM

Any diagnostic program must begin with a classification of disease and a sufficient number of proved cases to construct a data matrix. In 1959, the most accessible source of a large number of cases was the Central Office of the Veterans Administration, where the discharge diagnoses of the 5th admission to every VA hospital in the country could be obtained. At that time, the VA coded thyroid diseases according to the World Health Organization Classification. We found it convenient to begin with that classification (Table 1). In retrospect, we are glad to have begun with a simple classification which identifies the great majority of cases since it has been comparatively easy to modify our program for the rare disease as it is encountered.

It was next necessary to choose a suitable model for the logical process of diagnosis. It was obvious that the diagnosis of the diseases in the scheme depended upon evaluation of one or more of the following: (1) functional abnormality, (2) morphological abnormality, and (3) microscopic pathologic abnormality. Neither of the latter two categories is susceptible to electronic

TABLE I

WORLD HEALTH ORGANIZATION CLASSIFICATION OF THYROID DISEASE

250	Simple Goiter
251	Nontoxic Nodular Goiter
252	Thyrotoxicosis with or without Goiter
253	Myxedema and Cretinism
254	Other Diseases of the Thyroid Gland
194	Malignant Neoplasm of the Thyroid Gland

data processing at the present time, although ambitious efforts are now underway to examine roentgenograms of the chest¹ and scanograms of the thyroid¹ electronically. The evaluation of functional abnormalities of the thyroid gland is a more complex problem which is amenable to computer-aided calculations. The physician does not have and never has had access to a method for chemical or physical measurement of the functionally effective hormone fraction produced by the thyroid gland. It is now believed that the thyrometabolic status of an individual is determined by the circulating level of "free" thyroxine. This "free" thyroxine constitutes only a very small fraction (about 0.05 per cent) of the total amount of thyroxine present. Methods have been worked out for the determination of "free" thyroxine, but they are complex, time consuming and must be regarded entirely as a research procedure at this time. Free thyroxine levels are directly proportional to circulating thyroxine levels and inversely proportional to thyroid binding globulin (TBG) concentration. The thyrometabolic status will remain constant (that is, normal) as long as the ratio of plasma thyroxine to TBG remains the same. Thus, protein-bound iodine (PBI)

* From the Department of Radiology, University of Florida College of Medicine (L.T.F., C.M.W.) and Research Computation Center, University of Texas College of Medicine (J.E.O.).

TABLE II
SIGN, SYMPTOM AND LABORATORY DATA CONSIDERED BY PROGRAM

Age	Lethargic Movements	BMR
Sex	Cold Sensitivity	PBI, BEI or T ₄ by Column
Race	Decreased Sweating	
Nervousness	Decreased Appetite	6 hour I ¹³¹ Uptake
Heat Sensitivity	Weight Gain	24 hour I ¹³¹ Uptake
Increased Sweating	Increased Lethargy	T ₃ Resin Uptake
Increased Appetite	Dry Coarse Skin	TBG Level (thyroid-binding globulin)
Weight Loss	Facial Edema	
Hyperkinesis	Pain in Thyroid Gland	
Warm Moist Skin	Eye Signs	
Fine Finger Tremor		

determinations of 3, 5, and 12 μg per cent can all be compatible with euthyroid status when TBG levels vary similarly. Alterations in free thyroxine levels produce changes in pituitary secretion of thyrotrophin and hence in the rate of thyroxine production by the thyroid gland. Alterations of free thyroxine may occur as a result of non-thyrometabolic endocrine changes, such as the increase in circulating TBG resulting from pregnancy. Considerations identical to the statements which have been made about the PBI test apply to other measures of the thyrometabolic status of the patient, such as the radioactive T₃ resin uptake test which is a measure of the unsaturated TBG level, and the 6 and 24 hour thyroid I¹³¹ uptake test, which is usually a reflection of the rate of thyroidal synthesis of thyroxine, etc. Consequently, the physician is forced to rely upon his consideration of several signs, symptoms, and laboratory tests *because no single one of them reflects completely the factor which governs the over-all thyrometabolic status of the patient.* No one knows how a physician evaluates a suspected case of thyroid functional abnormality because the process is at least partially at an intuitive level which is heavily dependent upon previous experience.

THE DIAGNOSTIC-DECISION MODEL

Several theoretical models of the diagnostic-decision-making process were con-

sidered^{6,7,8,9,11} but finally discarded in favor of the conditional probability model. The conditional probability model, first suggested by Ledley and Lusted⁸ for the medical diagnostic process, has been found to be widely applicable and has been used successfully by many workers. The model has been described in detail in its application to thyroid functional abnormalities¹⁶ and need not be considered here.

THE DATA MATRIX

A data matrix consists of a table of the incidence of signs, symptoms, and laboratory values pertinent to the various abnormalities under consideration. These may be obtained from the literature or from inspection of actual case records. Although it is relatively easy to obtain values from the literature concerning the incidence of a particular symptom in a known disease, it is very difficult to obtain the incidence of that symptom in patients suspected of having a disease but who eventually prove not to have it. As a result, we elected to construct our original data matrix from the case records of patients referred to a Nuclear Medicine Laboratory for suspected thyroid disease, among whom a sufficient number was eventually found to be normal. Table II shows the list of signs, symptoms and laboratory tests considered by our program. In addition to these data, 34 commonly used drugs which the patient might have taken which would affect cer-

tain tests are considered and the affected tests are automatically deleted. Finally, entries for various types of morphologic abnormalities (multinodular goiter, solitary "cold" nodules, etc.) are present so that the probability of carcinoma may be given for each category.

MODIFICATION OF PROGRAM

In 1961, a review of consistent errors in the diagnosis of "masked" hyperthyroidism cases suggested a simple revision in the program, which ultimately led to their correct assignation. Inspection of our current computer-report format shown in Table III will make it easy to understand this revision. The program computes the probability of the three functional states (euthyroidism, hypothyroidism and hyperthyroidism), based on signs and symptoms, and their probability based on laboratory tests alone. At this point *in every case*, it goes

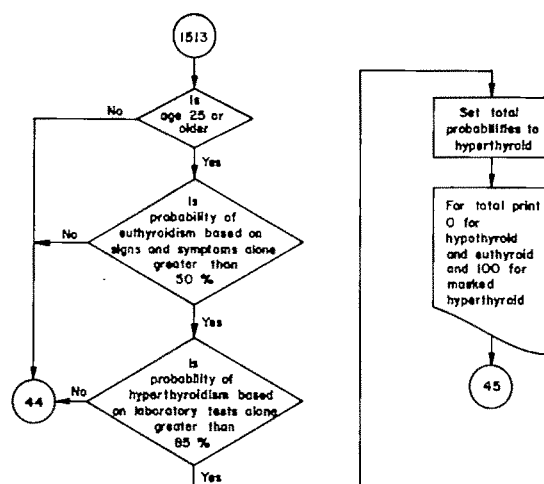


FIG. 1. Flow chart schematically showing logical subroutine for detection of cases of masked hyperthyroidism.

TABLE III

PRINT-OUT OF DIAGNOSIS OF THYROID FUNCTIONAL STATUS AND DIFFERENTIAL DIAGNOSIS
COMPUTER DIAGNOSIS OF THYROID
FUNCTION PATIENT 50000

Items		Per Cent Probability	Items Present
Signs and Symptoms	Hypothyroid	0	17
	Euthyroid	100	
	Hyperthyroid	0	
Laboratory	Hypothyroid	0	2
	Euthyroid	9	
	Hyperthyroid	91	
Total	Hypothyroid	0	
	Euthyroid	0	
	Hyperthyroid	100 (Masked)	
No Thyroid Disease			0
Simple Goiter (250)			0
Nontoxic Nodular Goiter (251)			0
Thyrotoxicosis (252)			100
Myxedema and Cretinism (253)			0
Other Diseases (Thyroiditis) (254)			0
Carcinoma of Thyroid (194)			0

through the logical steps shown in Figure 1. If the answer to the three questions is *yes*, then the machine prints out 0 per cent chance of hypothyroidism and euthyroidism and 100 per cent probability of masked hyperthyroidism. If the answer to any of these questions is *no*, then the possibility of masked hyperthyroidism is disregarded, and the program continues to the next step in the sequence (Step 44). These numerical dividing points were chosen empirically by examining our mistakes, and in our current series all masked hyperthyroids were correctly classified and no euthyroid individuals were misclassified. This separation of signs and symptoms from laboratory data has proved very useful in other areas, and we consider it significant that the physician is accustomed to considering the two bodies of data in a similar way when, for example, "the laboratory data just do not fit the clinical picture." The empirical figures we have chosen will undoubtedly be modified when a larger number of cases has been examined—but an experienced programmer can easily make the required alteration. *The essential value of the program is that in every case of possible thyroid disease examined by our program, the possibility of masked hyperthyroidism will be considered*

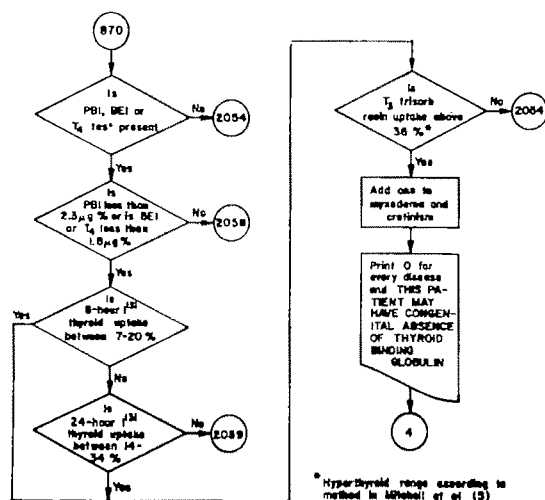


FIG. 2. Flow chart schematically showing logical subroutine for detection of cases of congenital absence or deficiency of thyroid binding globulin.

automatically, and we believe, recognized in a majority of cases.

Of special interest is a mistake in the diagnosis of a rare disease made by us, and the modification we have written for its recognition.

REPORT OF A CASE

A 1 year old Negro male with mental and growth retardation was observed to have lethargic movements and a dry, coarse skin. Laboratory tests included a cholesterol of 233 mg. per cent, a butanol extractable iodine of 1.4 µg. per cent, a 6 hour I^{131} uptake of 19 per cent and a T_4 trisorb resin uptake test of 42 per cent (this is within the hyperthyroid range). Computer diagnosis, with the above information, yielded a 91 per cent chance of hypothyroidism by signs and symptoms, a 63 per cent chance of hyperthyroidism by laboratory tests and a 52 per cent chance of hypothyroidism by all information combined. The patient's physician disregarded the laboratory values because of their apparently contradictory nature and administered exogenous thyroid with a dramatic improvement in the child's condition. Some months later, in reviewing our mistakes, this bizarre set of laboratory values suggested a diagnosis of congenital deficiency of thyroid binding globulin. A measurement of 8.4 µg. T_4 per cent TBG (normal range 12-20 µg. T_4 per cent) by the Bio-Science Laboratories confirmed this diagnosis.

A simple modification was written and added to our program (Fig. 2). When this modification had been added, 500 cases were re-examined and the program correctly assigned this case to the proper category and did not misclassify any other cases. As in the case of "masked" hyperthyroidisms, it will be necessary to modify these empirically chosen values when more cases have been encountered. Again, a major value of the program lies in the fact that this rare disease (the existence of which was unknown to the patient's physician) will be considered and *looked for automatically* in every case considered in the future by this program. The simplicity of construction of these modifications or subroutines is evident. Programmers of modest experience should have no difficulty in adding their own rare cases to the existing program.

We have recently added an accumulation subroutine to our program. The probability estimates of any specific sign, symptom, or laboratory value in our initial data matrix may be based on fewer than 100 cases. Because it is a laborious task to retrieve charts and data sheets, we have written a subroutine to enter the presence or absence of each symptom into the data matrix after the computer diagnosis of each. If each case is checked by a physician when the eventual outcome is evident, this program permits the automatic accumulation of probability estimates on signs and symptoms and laboratory tests based on a small number of entries. We have also written a program for the withdrawal of the sign and symptom entries when a mistake has been made in the diagnosis. Since a single case can only change the data matrix very slightly, many cases may be run before the mistaken diagnoses need be withdrawn. A run of 500 cases based on an 879 case data matrix failed to produce any different results, whether the program accumulated or did not accumulate. Both accumulation and non-accumulation programs are available in our recent publication.²

SUMMARY

A program, with flow-charts, for the diagnosis of thyroid disease based on experience gained with 1,379 cases of suspected thyroid disease has been written in Fortran II (for the IBM 709) and is available on request.* It makes use of a conditional probability model of medical diagnosis and is believed to imitate the thought processes of a physician experienced in thyroid disease. First, it evaluates the probability of a functional thyroid abnormality based on signs and symptoms alone; it then evaluates the probability of a functional abnormality based on the laboratory data, and finally considers all data together. Laboratory values and the probability values are routinely searched for some 10-15 specific combinations (such as those produced by acute thyroiditis, congenital deficiency of thyroid binding globulin, masked hyperthyroidism, etc.). If a particular test may give a conclusive diagnosis, it is requested and, if present, a specific diagnosis is printed out. After the diagnosis has been made, all values are entered back into the basic data matrix so that the subroutine changes the basic data matrix after each diagnosis. In this way, the program may be said to "accumulate experience." In the last 500 cases of suspected thyroid disease examined by the program at the University of Florida College of Medicine, 14 mistakes in the diagnosis of the thyrometabolic status were made (2.8 per cent) of which 7 could be corrected by easily written subroutines. We believe that the program is now ready for general use by other institutions and that it is in a form which can be easily modified for correction mistakes. It is only by the use of this program in a large number of institutions that the necessary number of rare cases can be encountered and appropriate additions to

the program made, in order to render the program truly useful to the physician.

Clyde M. Williams, M.D.
Department of Radiology
University of Florida
College of Medicine
Gainesville, Florida 32601

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* Request for this paper and the program should be addressed to L. T. Fitzgerald, Department of Radiology, University of Florida College of Medicine, Gainesville, Florida 32603.



SIMULTANEOUS INSULIN STUDY, THYROIDAL UPTAKE AND SCAN USING A SINGLE DOSE OF INSULIN I¹³¹*

By COSME R. CAGAS, M.D.,† CARL R. BOGARDUS, JR., M.D.,‡
and VERNON FICKEN, B.S.
OKLAHOMA CITY, OKLAHOMA

THE use of radioiodinated insulin has afforded another diagnostic tool in the evaluation of certain endocrine diseases in addition to diabetes mellitus. In a separate publication, we are presenting our data of its use in patients with thyroid disorders.³ In accordance with the principle of using the least radioactive dose possible, particularly in children, we have taken advantage of utilizing a single dose of insulin I¹³¹ to do an insulin degradation study, thyroidal uptake of radioiodine and scan simultaneously. This eliminates the necessity of having to give another dose of iodine I¹³¹ for the uptake and scan. The method herein described is not intended to replace the current use of unbound I¹³¹ preparation in which lesser amounts of radioactivity are employed for patients in whom thyroidal uptake alone is contemplated. This paper will deal with methodology and analysis of data obtained.

METHOD

After measurement of radioactivity by a scintillation counter, 10 to 25 μ c for adults and 5 to 10 μ c for children of insulin I¹³¹* with a specific activity of 5 mc/mg. are given intravenously. The remaining radioactivity in the emptied syringe is again counted and the dose given to the patient is calculated. Blood is drawn at the following times: 5, 10, 15, 20, 30, 60 and 120 minutes. The blood is allowed to clot at room temperature and is centrifuged. Radioac-

tivity is measured in 1 ml. of serum using a gamma well counter and the results are expressed in counts per minute per ml. of serum. The serum is precipitated with 8 ml. of 10 per cent trichloroacetic acid (TCA) followed by 2 washes with 8 ml. of 3 per cent TCA, essentially according to the method of Mahon *et al.*⁵ Radioactivity in the TCA-precipitable portion is then measured in the same way as the serum. For the purpose of this paper, unless specified otherwise, descriptions of disappearance of radioactivity pertain only to the TCA-precipitable portion.

Thyroidal radioiodine uptake and scanning are done in the conventional manner except for the use of radioiodinated insulin. With rare exceptions, some uptake can be measured as early as 120 minutes following injection of insulin I¹³¹. In the event that the uptake of radioactivity by the thyroid is deemed unnecessary or inadvisable, this can be blocked by potassium thiocyanate.

ANALYSIS OF DATA

Disappearance of radioactivity is characterized by an initial rapid phase followed by a prolonged slow phase.^{1,4} The nature of the curve precludes the determination of a true half-life. A theoretic count at zero time, representing 100 per cent, can be computed from the first two counts by the method of least squares ($\log Y = a + bX$). The first phase is defined by a straight line obtained by connecting the per cent concentrations at 5 and 10 minutes. By so de-

* Commercially available from Abbott Radio-Pharmaceuticals.

† From the Departments of Pediatrics and Radiology, Children's Memorial Hospital, University of Oklahoma Medical Center, Oklahoma City, Oklahoma.

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§ Chief, Section of Radioisotopes and Nuclear Medicine, Department of Radiology.

fining the first phase, a "half-life" may be derived. Since in the normal, the second phase starts at about 15 minutes, the slow phase can be similarly defined by connecting the per cent concentrations at 15, 20, 30, 60 and 120 minutes. By the same method, an intercept of the second phase at zero time can be computed and designated the letter "A." "A" reflects the rate of disappearance of the first phase (b_1) as well as the slope of the second phase (b_2). The curves are plotted semilogarithmically with the radioactivity expressed as per cent concentration per ml. of serum as the ordinate, as shown in Figure 1. An indication of degradation of insulin designated as "degradation index" is computed by multiplying the "half-life" in minutes by "A"

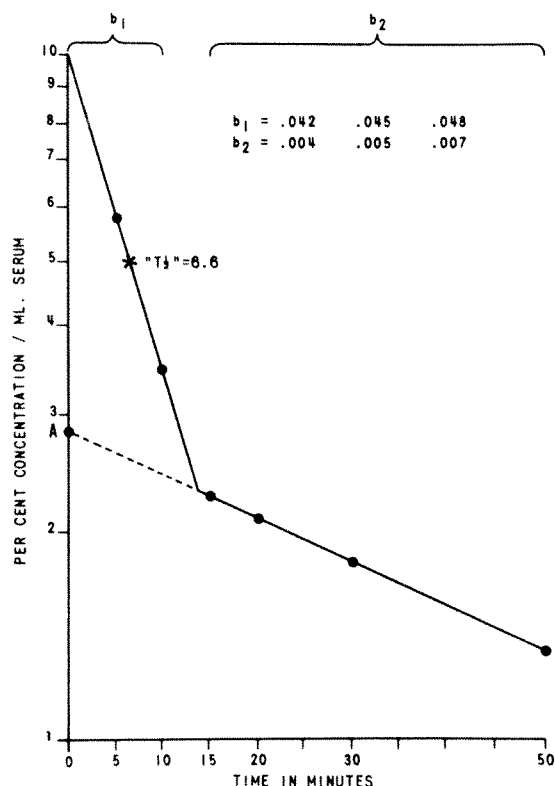


FIG. 1. The disappearance of radioactivity is characterized by a two-component curve plotted semilogarithmically. A "half-life" ($T_{1/2}$) is computed from the first (rapid) component and a "degradation index" is obtained by multiplying the "half-life" by "A." The curve shown is derived from 3 normal controls.

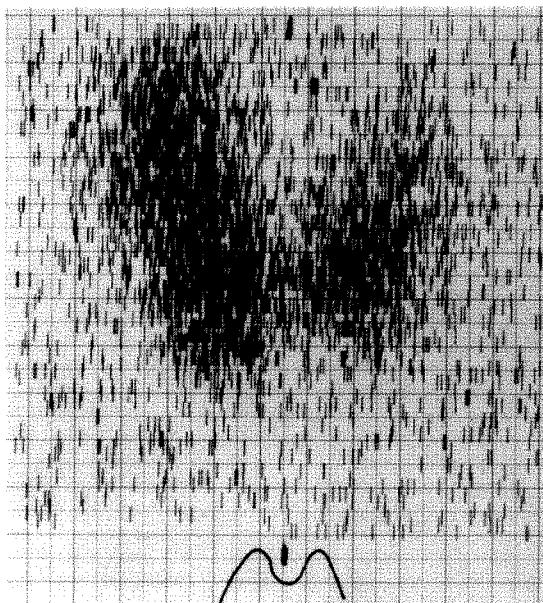


FIG. 2. Thyroid scan of a patient with hyperthyroidism 4 hours after a dose of $10 \mu\text{c}$ of insulin I^{131} . The 4 hour uptake was 92 per cent.

in per cent concentration of radioactivity in the TCA-precipitable portion of 1 ml. of serum. The "half-life" and the "degradation index" are inversely proportional to the speed of degradation, that is, the greater the value, the slower the rate of degradation.

DISCUSSION

The semilogarithmic plot employed, as shown in Figure 1, is adapted from the method of Bolinger *et al.*^{1,2} with some modifications. The idea of the "degradation index" has arisen out of the effort to show subtle differences among individual curves which could not be shown clearly by separate interpretations of the "half-life" and "A." Using this method, the normal values obtained from three control subjects showed a mean "half-life" of 6.6 minutes and a mean "degradation index" of 184. From the data thus far obtained from patients with thyroid and other endocrine disorders in addition to those of normal controls, a "half-life" of less than 6 and more than 7.4 minutes and a "degradation index" of less than 140 and more than 225

are suggestive of increase and decrease degradation, respectively. The significance of these and other aspects of the study beyond the scope of this paper will be published in detail elsewhere.⁸

As may be suggested by the "half-life" from the first phase as discussed above, labeled insulin is degraded rapidly. In the process of degradation, the labeling isotope is released as evidenced by the difference in the total serum radioactivity and in that of its TCA-precipitable portion. The free radioiodine is taken up by the thyroid gland and if the uptake is sufficient, thyroid scanning then can be performed. The thyroid scan shown in Figure 2 is that of a patient with hyperthyroidism. The uptake following 10 μ c of insulin I¹³¹ was 92 per cent in 4 hours. If thyroidal uptake is deemed unnecessary or inadvisable, this can be blocked effectively with an oral dose of potassium thiocyanate, 15 mg. per 100 ml. of extracellular fluid space given 30 minutes before the study.

Although all 3 procedures can be performed in most patients, there are exceptions to the use of insulin I¹³¹ for thyroidal uptake and scanning. A patient with a syndrome of myasthenia gravis, hyperthyroidism, subacute hepatitis and insulin-resistant diabetes showed an extremely prolonged "half-life." At the end of 24 hours, 38 per cent of the radioactivity remained bound to protein. If a thyroidal uptake had been done, the result would have been misleading, since only a portion of labeling material was available for uptake by the thyroid gland. A child with primary myxedema had an uptake of only 2 per cent in 24 hours. To outline the thyroid of this patient is virtually impossible unless one resorts to a much higher dose than we normally use.

CONCLUSION

The use of insulin I¹³¹ has afforded another parameter of evaluating certain endocrine diseases in addition to diabetes. In patients with thyroid disorders, an insulin degradation study can be performed simultaneously with thyroidal uptake of radioiodine and scanning when indicated, thus eliminating the necessity of a second dose of I¹³¹. The disappearance of radioactivity is plotted semilogarithmically and by the method of least squares ($\log Y = a + bX$), a "half-life" and a "degradation index" are computed from a two-component curve. These are inversely proportional to the degradation of radioiodinated insulin.

Cosme R. Cagas, M.D.
Department of Pediatrics
Children's Memorial Hospital
The University of Oklahoma Medical Center
800 Northeast 13th Street
Oklahoma City, Oklahoma 73104

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SIMULTANEOUS PAH, INULIN AND RENOGRAFIN- I^{131} RENAL CLEARANCE DETERMINATIONS AND A METHOD FOR CALCULATING RENOGRAFIN CLEARANCE FROM RENOGRAMS IN PATIENTS*

By I. MESCHAN, M.D., F. C. WATTS, B.S., E. LATHEM, M.D., W. H. BOYCE, M.D., H. E. SCHMID, M.D., C. D. MAYNARD, M.D., T. ROPER, M.D., and T. A. HOSICK, B.S.
WINSTON-SALEM, NORTH CAROLINA

IN PREVIOUS publications^{1,2,3} a close correlation has been shown between simultaneous inulin and renografin- I^{131} renal clearance in unanesthetized normal dogs. It was decided to continue this investigation in humans, both normal and those with various kinds of pathology of the vascular system or urinary tract. In each instance, by performing simultaneous inulin, para-amino-hippurate (PAH) and renografin- I^{131} clearances as well as ortho-iodo ^{131} -hippuric acid (OI ^{131} HA) and renografin- I^{131} renograms, it has been our purpose to: (A) assess further the correlation of inulin and renografin- I^{131} renal clearance in a variety of pathologic conditions in human beings; and (B) determine a method for quantitating the renografin- I^{131} renogram so that renografin clearance might be calculated from the renogram.

BASIC PHYSIOLOGICAL FUNDAMENTAL ANALYSES: THE ANALYSIS OF RENAL CLEARANCES IN A "COMPARTMENTALIZED SYSTEM"

Figure 1 illustrates the possible compartments with which we are dealing. The external circle is representative of the "field of vision" included by the scintillation probe, in the case of each kidney.

Compartment A may be considered as the major arterial compartment. This includes the renal artery, the dorsal and ventral branches of the renal artery, the arcuate artery, the inter- and intralobular

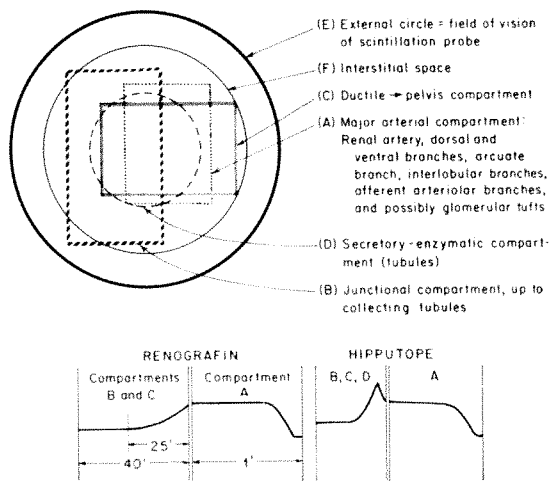


FIG. 1. Compartmental analysis for radioisotopic renogram.

branches, the afferent arteriolar branches and possibly even the glomerular tufts.

Compartment B, which overlies the first, may be called the junctional compartment between the arterioles, capillaries, and tubules, up to, but not including, the collecting tubules.

Compartment C may be called the ductile-pelvic compartment. In this compartment the urine, which has been formed in Compartment B, is concentrated to some extent and passes down ducts to the point of excretion from the kidney into the ureter.

There is, in addition, Compartment D, represented as a "secretory-enzymatic" compartment. In this compartment certain

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From the Departments of Radiology, Urology, and Physiology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.

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substances are secreted by the tubules into Compartments B and C by special enzymatic systems. It should be noted that, although this compartment would operate significantly with PAH and similar substances, it probably does not operate with inulin and inulin-like substances such as renografin (to any significant degree).

It will be noted that the external "field of vision" of the scintillation probe views many structures which are nonrenal, such as: the muscles of the flank, the skin and subcutaneous tissues, the suprarenal glands, perirenal fat and miscellaneous other tissues such as nerve tissues. In the case of the right kidney, the liver and/or gallbladder may be included in part and portions of the gastrointestinal system, along with the inferior vena cava and portal system. In the case of the left kidney probe, there are major arteries, such as the splenic artery, mesenteric arteries and the aorta. The spleen, the gastrointestinal tract, the left lobe of the liver and even the lung may be partially in view.

In addition, there are other factors such as aldosterone and antidiuretic hormone which have not been considered in the above compartmental analysis. The complexity of this system has led many investigators to the conclusion that quantitative analysis of the radioisotopic renogram is not "dependable."⁸

In recognizing the difficulties of this system, we have attempted to compensate as much as possible for the nonrenal components of Compartment E by the vascular probe centered over the heart or head, on the assumption that systemic circulation will, for the most part, reflect nonrenal blood pool events. We have also attempted, in many instances, to analyze this compartment by comparative simultaneous analyses of blood samples at the same time as a record over the heart pool has been made.

By using a compound such as renografin-I¹³¹, we virtually negate Compartment D, the secretory-enzymatic compartment.¹ We have attempted to obviate liver interference by avoiding a compound

such as diodrast which is in part secreted by the liver.⁵

There is a further compartment which includes the interstitium (Compartment F) throughout the entire body. Hopefully, in a state of equilibrium, this compartment forms the base line from which all further measurements are obtained. It is apparent, therefore, that by such analysis we may be able to reduce this complex physiologic apparatus to 3 compartments; and if Compartment A becomes negligible after a short period of time, since arterial flow is ordinarily rapid, it is conceivable that after this short period of time we may concentrate on Compartments B and C for our results.

In summary, there is a minimum of 6 and possibly 7 compartments, and we may utilize the following expedients to simplify our system:

- (1) An additional simultaneous record to achieve an approximation of nonrenal elements of one of these compartments (E): heart or head probe.
- (2) Choice of compound to eliminate from consideration one more of these compartments (D): renografin-I¹³¹.
- (3) Equilibration to establish a plateau state (F).
- (4) Time analysis to separate rapidly occurring events from those which occur later in physiologic sequence (A from B+C).

By obtaining sequential blood determinations, we may achieve a further understanding of events in Compartment E. It has been our experience that close agreement between such sequential blood determinations and the heart or head probe is usually obtained.

By separate analysis of arterial events in the first 1 minute, we can for the most part assume that Compartment A graphically becomes relatively small except in those instances where arterial flow is slow and impaired. By consideration of PAH clearance along with the OI¹³¹HA renogram, we achieve an understanding of effective renal plasma flow.⁵ Where such flow is known to

be impaired, we know that our compartmental analysis must be more complicated.

By this process of elimination and analysis, we can narrow our consideration to Compartments B and C, except where renal plasma flow is delayed. It will be shown in present results that Compartments B and C, when subjected to exponential analysis, follow rather closely a single exponential equation in most normal cases.

It is our future plan to separate a sufficient number of abnormal cases from the normal so that this compartmental analysis can be carried forward by means of analog computer techniques. The results thus far have been particularly encouraging in those cases which have normal clearances, and the model that we are proposing is especially suitable for analog computer analysis.

DESCRIPTION OF PATIENT POPULATION STUDIED

Patients with a wide variety of diagnoses were studied. Any patient who had a catheter in one ureter and a second catheter in the urinary bladder could be subject to a split-function study relative to each kidney. These patients had the following primary diagnoses: cystitis, pyelonephritis, glomerulonephritis, renovascular hypertension, essential hypertension, renal calculi, ureteral calculi, renal artery aneurysm, carcinoma of the urinary bladder, hypoplastic kidney and ureteropelvic obstruction.

In all, there were 72 patients. In 24 of these patients, simultaneous inulin, PAH and renografin- I^{131} split-function clearance studies were performed. In the remaining 48 patients, clearance studies were the sum of both kidneys, and an effort was made from the radioisotopic renograms obtained by separate recordings over each kidney to determine the summated calculated renografin- I^{131} clearance.

BASIC CLEARANCE PROCEDURES WITH PATIENTS

Inulin and Renografin Priming: Use 10 per cent inulin, purified (U. S. Standard

Products), 50 mg./kg. body weight, 0.5 cc. renografin intravenously.

Para-aminohippuric Acid (PAH) Priming: Use 20 per cent PAH (of sodium salt) (Sharpe and Dohme products); 8 mg./kg. body weight.

Sustaining Solution at 3 cc./min.: 600 cc. isotonic normal saline-sterile;* 54 cc. inulin 10 per cent solution; 10 cc. PAH 20 per cent solution; 5 cc. renografin solution.

DETAILED PROCEDURE

1. Prepare sterile priming and sustaining solutions.
2. Hydrate the patient—6.28 cc. per pound (or 15 cc./kg.) of body weight—1 to 2 hours prior to procedure. Maintain with 150 cc. of water every half hour thereafter throughout the test. In patients with catheters *in situ*, the intravenous drip technique for hydration is preferred, and under these circumstances, 40 to 60 drops per minute, 5 per cent glucose in water. This is begun 1 to 2 hours before the test, and maintained throughout the test period.
3. Start an intravenous infusion (if not already begun as in 2 above), counting the drop rate at 40 to 60 drops per minute. This is the sustaining solution and represents a separate intravenous infusion from 2 above.
4. Inject inulin, renografin and PAH priming solution into the intravenous tubing and record time.
5. Wait 45 minutes, checking the intravenous site frequently for infiltration of subcutaneous tissue. Five minutes before the first clearance period is to begin, inject renografin- I^{131} , 10 μ c per patient, and obtain a renogram recording.
6. In patients who do not have a catheter in the urinary bladder, have the patient empty the bladder. Discard this urine and immediately start the first clearance period recording the time started. In patients with a catheter in the urinary bladder, withdraw all urine from the urinary bladder and replace collection bottle, beginning with one bottle at the time of the first collection period. The collection periods are 20 minutes

* In some patients, 600 cc. isotonic glucose in water (5 per cent dextrose-sterile) was used instead.

each and each bottle is carefully marked. A minimum of three 20 minute clearance periods is thus obtained.

7. Insert an indwelling needle in a vein for withdrawal of blood samples. Three to 5 cc. blood samples are drawn at 2 to 5 minute intervals, as feasible, and at least one 10 cc. sample is obtained in the middle of each 20 minute clearance period. The blood is immediately placed in a heparinized tube and aliquots are withdrawn for hematocrit determination, for scintillation radioactive assay, and for inulin and PAH blood level determinations.

8. If the patient does not have an indwelling catheter in the urinary bladder, the patient is asked to void after 20 minutes and the time is recorded. With an indwelling catheter in the urinary bladder, the 20 minute collection period is carefully marked and a new specimen is begun each 20 minute interval for three such intervals.

9. In those patients with an additional catheter in one ureter, simultaneous collections from this catheter are made with those from the catheter in the urinary bladder.

10. The scintillation probes are placed as follows: (a) two balanced probes, one over each kidney; (b) a third probe over the heart to monitor blood pool. In certain instances, this third probe was placed over the head of the patient; and (c) in certain instances also, a fourth probe has been utilized to monitor the urine collection in the urinary bladder. Quantitation by such a probe has been shown by us to be at least equally as accurate as the urine collection and more accurate where prostatic or urethral obstruction or any cause for urinary bladder retention is present.

OBSERVATIONS

From the renograms and heart probe, the following observations were made and recorded:

A. PAH, inulin and renografin- I^{131} renal clearance determined conventionally.

B. Qualitative assay of the $OI^{131}HA$ and renografin- I^{131} renograms as either abnormal or normal.

C. Renografin- I^{131} clearance as calculated from a single exponential function, where applicable (clearance coefficient μ).

D. Clearance as calculated from the second exponential where the curve of clearance is best represented by summation of two exponentials. (Exponential B for the fast component of the curve, and exponential D for the slower component respectively).

E. Urine flow and square root of urine flow.

F. Filtration fractions:

$$\frac{\text{inulin}}{\text{PAH}}; \quad \frac{\text{renografin-}I^{131}}{\text{PAH}}$$

G. Exponentials B and D for the "heart probe" which recorded the rate of disappearance of the radioactivity from the blood.

H. History, clinical diagnosis, findings on physical examination, urinalysis, blood chemistries, and special studies were also recorded.

METHOD OF CALCULATING CLEARANCE FROM THE RENOGRAFİN- I^{131} RENOGRAFİN EMPLOYING A SINGLE EXPONENTIAL FUNCTION, μ , AS THE COEFFICIENT OF CLEARANCE AND THE HALF-TIME OF CLEARANCE

This method assumes that the renografin- I^{131} renogram clearance curve obeys the general biologic equation:

$$(1) \quad Y_t = Y_0 e^{-\mu t}, \text{ where:}$$

Y_t = activity over the kidney at any time, t

Y_0 = activity over the kidney at time t_0

μ = regression coefficient or the coefficient of clearance

t = time elapsed after t_0 .

The above equation may be solved for time when the activity has diminished to 1/2 its initial value in accordance with the following equation:

$$(2) \quad t_{1/2} = \frac{-\ln 1/2}{\mu}, \text{ where:}$$

$-\ln 1/2 = -$ the natural logarithm of $1/2$, 0.693.

In a similar manner we may solve equation (1) for μ as follows:

$$(3) \quad \mu = \frac{\log Y_t/Y_0}{t}.$$

For computation purposes, the values of Y_t at the various values of t were run through a Model 1620 computer (IBM) from which the μ values were determined. The half-time values were determined by equation (2).

The clearance values for each patient were then related to the corresponding half-time values in the following manner:

$$(4) \quad C \propto \frac{1}{t_{1/2}}.$$

From this relationship it also follows that:

$$(5) \quad C \propto \frac{1}{\frac{-\ln 1/2}{\mu}}; \text{ substituting the denominator value for } t_{1/2} \text{ as derived in equation (2)}$$

(6) $C \propto \frac{\mu}{-\ln 1/2}, \text{ or } \frac{\mu}{+0.693}.$

In order to arrive at a proportionality constant that has some basis in logic, the inulin clearance values for 17 cases were related directly to 1,000 times the reciprocal of the clearance half-time. The clearance values were, in each case, approximately twice the reciprocal of the half time $\times 1,000$. (The "1,000" can be justified on the basis of the arbitrary strip chart paper units which are expressed in values from .02 to 1.0 and from which the data for the half-time were determined.)

By regression studies with the Model 1620 IBM computer, it was determined that the curve produced by the renografin- I^{131} renogram in approximately two-thirds of the cases best fitted a single rather than a double exponential equation. Since the value 2+ continually came into view, by almost any means of analysis, it was de-

cided to test "e", the natural logarithm base as follows:

$$(7) \quad C = K \frac{\mu}{-\ln 1/2}, \text{ and } K \text{ as } 1,000 \cdot e^{-\ln 1/2} \\ = \frac{1,000 e^{-\ln 1/2} \mu}{-\ln 1/2},$$

$$(8) \quad C = \frac{2,000 \mu}{.693},$$

$$(9) \quad C = 2,886 \mu.$$

This empirically determined proportionality constant was then applied to the individual cases and was found to be reasonably accurate in clearance determination as will be described below. (It does, however, appear that the true equation of the normal renografin- I^{131} renogram curve should be adjusted by the addition of a second constant in order to determine more accurately the true clearance values. This new constant will perhaps be based upon some function of the urine flow in approximately one-third of the cases.)

EXPLANATION OF RESULTS

In every instance, the assumption has been made that the PAH and inulin clearance determinations represent an accurate basis for all comparison. This is justified by virtue of extensive experience which our laboratories have had in PAH and inulin clearance determinations over several thousand experiments in unanesthetized dogs and a period of approximately 5 years.

Table 1 presents the renal function in normal man according to Smith⁴ and the corrected values for our laboratory, based upon correlation with dog data (per 1.73 m.²). The normal values indicated here were obtained as follows: Over a period of years, a large number of studies in unanesthetized trained dogs has been done. These data have included approximately 2,000 clearance determinations on 50 trained dogs. Usually, clearances were performed at 3 to 5 consecutive 10 minute periods each in conventional fashion by the technique of Homer W. Smith. Our previous reports have included many of these. From the data

TABLE I
RENAL FUNCTION IN NORMAL MAN ACCORDING TO HOMER W. SMITH⁴ AND CORRECTED VALUES
FOR OUR LABORATORY, BASED UPON CORRELATED DOG DATA (PER 1.73 M.²)

	Males		Females	
	H. W. Smith	Our Laboratory	H. W. Smith	Our Laboratory
Clearance Inulin cc./min.	124 ± 25.8	97.3 ± 20.2	109 ± 13.5	85.5 ± 10.6
Clearance PAH cc./min.	654 ± 163	568 ± 142	592 ± 153	515 ± 133
Inulin/PAH Filtration Fraction × 100	19.2 ± 3.5	17.1 ± 3.1	19.4 ± 3.9	16.6 ± 3.5

The tentative values we have accepted for renografin are 37 ± 5 for each kidney.

so included, it has been determined by one of us (H. E. Schmid, M.D.) that the relationship of our values on normal dogs to those published by Homer W. Smith have been:

$$\frac{\text{Clearance Inulin, Our laboratory}}{\text{Clearance Inulin, Homer W. Smith}} = .785 \text{ in cc./min.}$$

$$\frac{\text{Clearance PAH, Our Laboratory}}{\text{Clearance PAH, Homer W. Smith}} = .87 \text{ in cc./min.}$$

In order to arrive at a normal value for patients, we have made an identical correction for the "man values" presented by Homer W. Smith and these in turn are presented in Table I. The renografin-I¹³¹ clearance values as indicated in this table were obtained on the basis of simultaneous determinations of renografin-I¹³¹ and inulin in the unanesthetized normal dogs, and making appropriate correction for man.

CORRELATION OF PAH, INULIN AND RENOGRAFIN-I¹³¹ CLEARANCE VALUES IN SPLIT-FUNCTION STUDIES WITH ONE ANOTHER (TABLE II)

It will be noted by reference to Table II, that PAH and inulin clearance values were well correlated with one another on the same side (coefficient 0.66 in 43 determinations). A similar significant correlation was obtained between PAH and renografin-I¹³¹ clearance determined conventionally (0.585 in 41 cases and 0.46 when calculated as described above). There was a good inverse correlation of PAH clearance with the fil-

tration fraction

$$\frac{\text{inulin}}{\text{PAH}}$$

on the same side and also with

$$\frac{\text{renografin-I}^{131}}{\text{PAH}}$$

on the same side. The PAH clearance appeared to be influenced by the urine flow (correlation coefficient 0.485 in 41 cases). It is noteworthy that the correlation coefficient of PAH with inulin clearance approached the correlation coefficient of PAH with renografin-I¹³¹ determined conventionally and renografin-I¹³¹ calculated.

It is highly significant that the correlation coefficient of inulin clearance with renografin-I¹³¹ clearance on the same side was 0.845 in 42 cases. *We may presume that for clinical purposes, renografin-I¹³¹ clearance may be substituted for the more burdensome inulin clearance studies.*

The correlation coefficient for renografin-I¹³¹ clearance as determined against that calculated was 0.52 for all cases, both normal and abnormal ($p < .01$).

It is interesting to study the relationship of the various coefficients of clearance with renografin-I¹³¹ clearance values:

The correlation coefficient of the μ coefficient of clearance, which represents the coefficient from a single exponential type equation, is 0.48 ($p < .01$).

There is an inverse correlation with the renal half-time clearance on the same side (-0.415) ($p < .02$).

TABLE II
CORRELATION COEFFICIENTS OF PAH, INULIN AND I¹³¹ RENOGRAFIN CLEARANCE
VALUES IN SPLIT-FUNCTION STUDIES*

Correlation Coefficient of PAH Clearance with:	Level of Significance (p value)		No. of Determinations
.66	< .001	Inulin clearance	43
.585	< .001	Renografin-I ¹³¹ clearance determined directly	41
.46	< .02	Renografin clearance calculated	24
-.56	< .001	I/PAH	43
-.535	< .001	R/PAH	39
.485	.001	Urine flow	41
.425	< .01	Square root urine flow	41
.435	< .05	Clearance coefficient, μ	25
Very poor		<i>B</i> coefficient on heart probe	18
Very poor		<i>D</i> coefficient on heart probe	18
-.40	< .05	Half-time of kidney excretion of renografin-I ¹³¹	25
Very poor rt. +.04; lt. -.22)		Blood urea nitrogen	27
Correlation Coefficient of Inulin Clearance with:			
.845	< .001	Renografin-I ¹³¹ clearance	4
.515	< .001	Actual urine flow	41
.41	< .01	Square root urine flow	41
-.295	> .1	<i>B</i> coefficient of heart probe curve	18
Poor		<i>D</i> coefficient of heart probe curve	18
Very poor		Blood urea nitrogen	27
Correlation of Renografin- I ¹³¹ Clearance Determina- tion Conventionally with:			
.48	< .01	μ coefficient same side	27
-.415	< .02	T _{1/2} kidney, excretion renografin-I ¹³¹	27
.52	< .01	Renografin clearance calculated	26
-.235	> .1	Blood urea nitrogen	29
Clearance Coefficient Reno- grafin-I ¹³¹ Renografin Clear- ance Calculated from Reno- grams with:			
.265	< .1	Urine flow, same side	41
.22	> .1	Square root urine flow, same side	41

* Definitions for Tables II, III, IV and V:

Clearance coefficient = μ in following equation:

$$Y_t = Y_0 e^{-\mu t}, \text{ as in text.}$$

Clearance coefficients *B* and *D* refer to coefficient in summation of exponential

$$Y_t = Ae^{-Bt} + Ce^{-Dt}.$$

B and *D* coefficients from heart probe curve also refer to summation of two exponentials, same equation as summation of two exponentials for kidney probe.

The double exponential coefficients are not nearly as well related to renografin-I¹³¹ clearance in most instances. On a theoretical basis we would have expected that perhaps the *D* coefficient of clearance would have yielded a more favorable result than

TABLE III
FURTHER CORRELATION COEFFICIENTS OF FILTRATION FRACTIONS

Correlation of I/PAH with Respect to:	Level of Significance (p value)		No. of Determinations
.825	<.001	R/PAH on same side	39
-.245	>.1	Urine flow on same side	41
-.30	.05	Square root urine flow, same side	41
Correlation of R/PAH with Respect to:			
-.365	.02	Actual urine flow, same side	39
-.435	<.01	Square root urine flow, same side	39

is indicated.

CORRELATION COEFFICIENTS OF FILTRATION
FRACTIONS (TABLE III)

The filtration fraction

inulin

PAH

has an excellent correlation with

renografin-I¹³¹

PAH

on the same side (0.825). This further strengthens the concept that renografin-I¹³¹ clearance determined conventionally as described, can, for all practical clinical purposes, be substituted for inulin clearance; and if one obtains a simultaneous PAH

clearance determination, a filtration fraction can be predicted in most instances. The accuracy of this filtration fraction determination is affected only to a slight extent by urine flow or the square root of urine flow on the same side.

CORRELATION COEFFICIENTS OF THE VARIOUS RE-
GRESSION COEFFICIENTS OBTAINED FROM RENO-
GRAFIN-I¹³¹ RENOGRAMS (TABLE IV)

The right and left renografin-I¹³¹ clearances were well correlated with one another and seem to follow the single exponential type equation (correlation coefficient, 0.71 in 10 cases). On the other hand, the summation of two exponentials did not give quite as good agreement between the right and left side. The clearance coefficient, μ , was not well correlated with the heart probe

TABLE IV
CORRELATION COEFFICIENTS OF VARIOUS COEFFICIENTS OF CLEARANCE OBTAINED
FROM RENOGRAPHIN RENOGRAMS

Correlation of μ Coeffi- cient of Renogram on One Side with:	Level of Significance (p value)		No. of Determinations
Very poor		B coefficient renogram curve	17
.72 rt., -.22 lt.	rt. <.001; lt. 1	D coefficient renogram curve	17
.385	<.1	B coefficient heart probe curve	19
.395	<.1	D coefficient heart probe curve	19
Very poor		1/2 time, heart probe curve	20
-.90	<.001	1/2 time, kidney renografin-I ¹³¹ clearance	17
.9998	<.001	Renografin clearance calculated 1/2 time	26
Very poor		blood clearance by serial samples	
-.195	>.1	Blood urea nitrogen	27

TABLE V
CORRELATION COEFFICIENTS OF $T_{1/2}$ OF EACH KIDNEY'S RENOGRAM

One-half Time Each Renografin Renogram Correlated with:	Level of Significance (p value)		No. of Determinations
Very poor		1/2 time heart probe curve	20
-.91 rt.; -.89 lt.	<.001	Renografin clearance calculated	15 rt.; 11 lt.
-.90	<.001	μ coefficient renogram	27
Very poor		B coefficient renogram	17
.38	.1	D coefficient renogram	17

curve when this curve was expressed as a summation of two exponentials with a correlation coefficient of 0.39 ($p < .1$).

There is, of course, an excellent inverse correlation of the clearance coefficient, μ , and the renal clearance half-time. This is inherent in the algebraic consideration. The perfect correlation between the single exponential coefficient, μ , and renografin- I^{131} clearance as calculated by use of this exponential is merely a check upon the accuracy of the calculation.

In those cases where the renogram seems to follow a summation of two exponentials rather than the single exponential equation, the first coefficient of clearance B correlated poorly with the D coefficient on the same side (correlation coefficient, 0.37 in 17 cases), and very poorly with all other coefficients considered, with the half-time of renal clearance, with the half-time of the heart probe curve, and with renografin- I^{131} clearance as calculated above. It is apparent from this analysis that: where the renogram curve appears to follow a single exponential function, fair accuracy is derived in calculating renografin- I^{131} clearance from the renogram. However, when one attempts to calculate clearance from the renogram curve which follows the summation of two exponentials, confusing results are found.

CORRELATION COEFFICIENT OF THE HEART PROBE
DISAPPEARANCE CURVES WITH RENOGRAFIN- I^{131}

In most instances, the disappearance curves as obtained by a probe over the heart appeared to follow a summation of two exponentials. In only one instance could this curve be expressed by a single

exponential equation. In general, the data obtained from the heart probe could not be related in meaningful fashion to a calculation of renografin- I^{131} clearance.

CORRELATION COEFFICIENTS OF THE HALF-TIME
OF CLEARANCE OF EACH KIDNEY AS OBTAINED
FROM THE RENOGRAM (TABLE V)

The half-times of clearance as obtained from the renogram for each kidney correlated well in inverse fashion with the single exponential coefficient, μ , (correlation coefficient, -0.90 in 27 cases). There was only a fair to poor correlation of the half-time of clearance with the D coefficient in those renograms which were best expressed by summation of two exponentials (0.38 in 17 cases).

From these various data, the following conclusion is justified: The most accurate expressions of renografin- I^{131} clearance which can be obtained from the renogram are: half-time of clearance; the μ coefficient when the renogram curve follows a single exponential equation; and renografin- I^{131} clearance, calculating this from the half-time of clearance and μ coefficient of clearance.

THE ACCURACY OF COMBINED CLEARANCE VALUES
FOR INULIN, PAH AND RENOGRAFIN- I^{131} WHEN
BOTH KIDNEYS ARE SUMMATED

The combined clearance values do not, of course, express individual kidney function, but rather represent the summated function of both kidneys together. We may, however, test the accuracy of our method by comparing simultaneous PAH, inulin and renografin- I^{131} clearances. Although the number of cases so studied is relatively

TABLE VI
THE SIGNIFICANCE OF THE RENOGRAM IN RELATION TO DETERMINED CLEARANCE

	PAH, Inulin and Renografin Clearances Agree	PAH Alone Disagrees	PAH and Inulin Disagree	Inulin Alone Disagrees	Renografin Clearance Alone Disagrees	All 3 Clearances Disagree	Inulin and Renografin Together Disagree
Normal Renografin Renogram Total 26	17 (65.4%)	6 (23.1%)	0	1 (3.9%)	0	2 (7.7%)	0
Abnormal Renografin Renogram Total 13	5 (38.5%) Capital O (stands for ortho I ¹³¹ hippuric acid)	0	1 (7.7%)	0	2 (15.4%)	3 (23.0%)	2 (15.4%)
Normal OI ¹³¹ HA Renogram Total 23	15 (65.2%)	4 (17.4%)	1 (4.3%)	1 (4.3%)	0	2 (8.7%)	0
Abnormal OI ¹³¹ HA Renogram Total 9	2 (22.2%)	0	1 (11.1%)	0	1 (11.1%)	3 (33.3%)	2 (22.2%)
Total 71	39 (54.9%)	10 (14.1%)	3 (4.2%)	2 (2.8%)	3 (4.2%)	10 (14.1%)	4 (5.6%)
OI ¹³¹ HA and Renografin Renogram Normal Total 21	14 (66.7%)	4 (19.0%)	0	1 (4.8%)	0	2 (9.5%)	0
OI ¹³¹ HA Normal; Renografin Renogram Abnormal Total 2	0	0	0	1 (50%)	1 (50%)	0	0
OI ¹³¹ HA and Renografin Renogram Abnormal Total 7	2 (28.6%)	0	1 (14.3%)	0	1 (14.3%)	2 (28.6%)	1 (14.3%)
OI ¹³¹ HA Renogram Abnormal; Renografin Renogram Normal Total 2	1 (50%)	1 (50%)	0	0	0	0	0
Total 32	17 (53.1%)	5 (15.6%)	1 (3.1%)	2 (6.3%)	2 (6.3%)	4 (12.5%)	1 (3.1%)

small, there is a tendency for corroboration of the more significant data previously described for individual kidneys.

THE SIGNIFICANCE OF THE RENOGRAM IN RELATION
TO RENAL CLEARANCE (TABLE VI)

It is important to try to relate quantitative data from simultaneous clearance determinations with our qualitative under-

standing of both the renografin-I¹³¹ renogram or the ortho-iodo¹³¹-hippuric acid renogram. The qualitative evaluation of either the renografin-I¹³¹ renogram and the ortho-iodo¹³¹-hippuric acid renogram agreed closely with the three clearances performed in approximately 54.9 per cent of the cases. The agreement was closer in those instances where the renograms were normal than

where they were abnormal. Thus, where the renograms were normal, the three clearances were also normal in two-thirds of the cases; but where either renogram was abnormal, the agreement with clearance occurred in 38.5 per cent of cases for the renografin- I^{131} renogram, and only 22 per cent of the cases for the ortho-iodo I^{131} -hippuric acid renogram. In most instances, the PAH clearance reflected this disagreement either by itself or in combination with one or the other of the two clearances performed. Thus, out of the total 32 cases in which disagreement occurred, PAH disagreement occurred in 23 cases (over two-thirds).

In analyzing the renografin- I^{131} and ortho-iodo I^{131} -hippuric acid renograms in relation to clearance, there is very little difference noted between their accuracy in predicting clearance.

When the two types of renograms were considered together in any given case, both types, where normal, agreed completely with the clearances in two-thirds of the cases. There were 7 instances where both types of renograms were abnormal and in these 7 instances, complete agreement with the clearances was obtained in only 2 cases. In 4 of the 5 cases in which disagreement occurred, the renografin- I^{131} clearance was normal despite the abnormal qualitative renografin- I^{131} renogram. The inulin clearance was in agreement with the renografin- I^{131} clearance in 3 of these 4 cases.

SUMMARY

1. Even when both ortho-iodo I^{131} -hippuric acid (OI I^{131} HA) and renografin- I^{131} renograms are normal qualitatively, the PAH, inulin and renografin clearances are normal in only two-thirds of the cases.

2. When the renograms are normal, and one or another of the clearances is abnormal, it is usually the PAH clearance which proves to be abnormal.

3. Where the renograms are qualitatively abnormal, one or another of these three clearances may be normal. In a high proportion of these, all three clearances may be normal despite the abnormal renogram of either type.

4. Where separate clearance determinations from each kidney are feasible, there is a definite contribution to an understanding of the kidney function which can be contributed by these clearance values, in addition to the qualitative analysis of the renograms. Since it would appear that a renografin- I^{131} clearance can be calculated from a renografin- I^{131} renogram in a significant number of cases, it would be important to attempt and record such calculation.

I. Meschan, M.D.

Department of Radiology

The Bowman Gray School of Medicine

Wake Forest College

Winston-Salem, North Carolina 27103

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RADIOISOTOPIC SCANNING AS AN AID IN PLANNING RADIATION THERAPY*

By M. TEFFT, M.D.
BOSTON, MASSACHUSETTS

SEVERAL authors have described the use of colloidal Au^{198} for radioisotopic scans of the liver to evaluate liver abnormality and position.^{2,4,5,6,7} Mercurial diuretic compounds, such as neohydrin and chlormerodrin, tagged with either the radioisotope Hg^{203} or Hg^{197} , have been used to demonstrate replacement of renal tissue by mass lesions and, to a lesser extent, renal function.^{1,7,8}

The combined value of these scans seemed to us to include the localization of these organs in relation to the area encompassed by radiation therapy. More specifically, we have found such scans to be useful where irradiation is directed to the liver and a method of sparing the underlying kidney is sought. We have selected the following case to illustrate this.

ILLUSTRATIVE CASE

B.M. was a 6 year old boy who underwent removal of a left Wilms' tumor, postoperative irradiation of the left renal fossa and intravenous actinomycin D, at another hospital. Within 4 months, he developed both pulmonary metastases and a mass in the right upper quadrant which was considered to be due to a liver metastasis. He was admitted to The Children's Hospital Medical Center and was found to have a mass in the right upper quadrant, 5 cm. below the right costal margin, and in the midclavicular line. The remainder of his physical examination and the laboratory examination were not remarkable.

A liver scan using Au^{198} was made in both the anterior and right lateral projections; 150 μc of the colloidal compound (3 μc per kg. of body weight) was injected intravenously and 4 hours later scanning was performed. A Picker Magnascanner was used. This was equipped with a pulse height analyzer and a 19 hole lead-shielded collimator. The factors used were: a lower and upper "window" of 361 and 461,

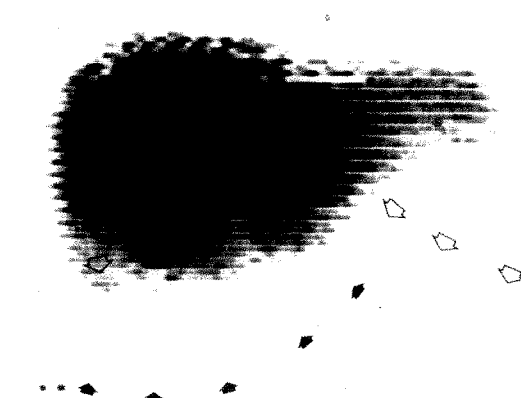


FIG. 1. Anterior scan of the liver showing "serration" along the inferior border of the liver. Black arrows represent the edge of the palpable mass as transposed to the scan at the time of the examination. White arrows indicate the last palpable anterior ribs. A diagnosis of liver metastasis was made.

respectively, on the analyzer; a scan speed of 24 cm./min.; a line spacing of 0.3 cm.; the voltage of the photorecord system was set at 1,500 volts for an average maximum count rate of 8,000 per minute; 1,200 volts was selected for one-half of the maximum counts. The probe high voltage of 559 volts is a function of the individual unit and calibration to the isotope; the density setting of 50 is a function of calibration to film processing.

Anatomic landmarks were demarcated on the skin and recorded on the teledeltos paper scan; a photorecord scan was made simultaneously with the paper scan. For the anterior scan, landmarks were the xyphoid, last palpable lower ribs, iliac crests and several marks on the skin on the lateral abdominal walls. Landmarks for the lateral scan were the last palpable rib and iliac crest on the side nearest the crystal and several marks on the tangential skin on the anterior and posterior abdominal wall.

At the completion of scanning, the area oc-

* From the Department of Radiology, The Children's Hospital Medical Center, and from the Department of Radiology, Harvard Medical School.

cupied by functioning liver tissue was demarcated on the skin by reference to the teledeltos paper scan. The portion not demarcated by scan, the region of the palpable mass, was marked on the skin by palpation and recorded on the scan (Fig. 1). Lead markers were placed on the skin at the points of reference and a roentgenogram was obtained at 6 feet from tube to patient. This was compared to the portal roentgenogram obtained at the start of radiation therapy and thus the anatomic volume treated was recorded.

With the area encompassed by the liver now demarcated by ink marks on the skin of the anterior and posterior abdominal walls, radiation therapy, in conjunction with actinomycin D, was directed to the entire volume of both the lungs and liver in continuity. Orthovoltage technique with 250 kv. peak, 15 ma., 80 cm. target skin distance and a half value layer of 2.6 mm. Cu with filter of 0.4 mm. Sn, 0.25 mm. Cu and 1 mm. Al was used. Opposed anterior

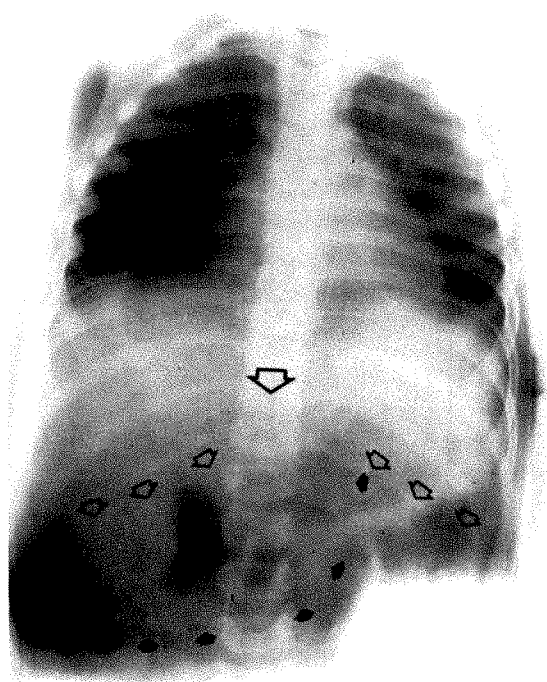


FIG. 2. Anterior portal film showing irradiation directed to the entire volume of both of the lungs and to the volume of liver as demarcated by scan and abdominal palpation. The central white arrow shows the xyphoid. As before, the solid black arrows and white arrows indicate the palpable mass and the last palpable anterior ribs, respectively.

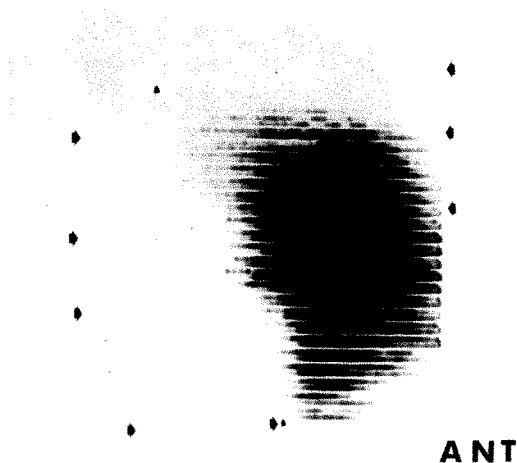


FIG. 3. Right lateral view of the liver scan. There is diminution of uptake in the inferior border of the liver at the site of the palpable mass. The liver is noted to lie anterior and just beneath the anterior abdominal wall. Black arrows demarcate skin marks on the anterior and posterior abdominal walls.

and posterior portals were irradiated. (Fig. 2).

When the lungs and liver had received 1,200 rad in 10 elapsed days, a higher additional dose of 1,800 rad in 15 elapsed days was planned to the liver. In order to evaluate the position of the solitary right kidney, 100 μ c of Hg^{197}

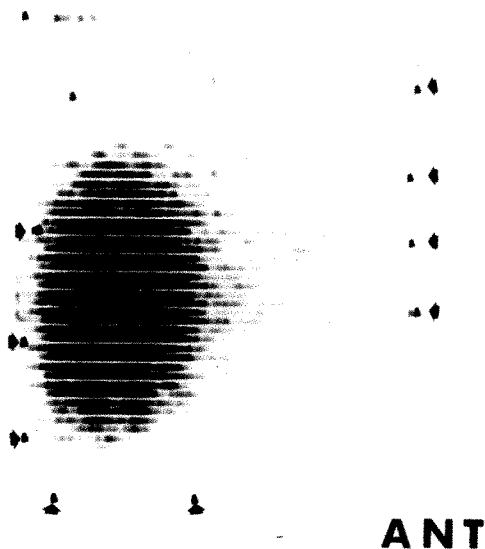


FIG. 4. Right lateral renal scan. The kidney is noted to lie in a posterior position. Once again, black arrows demarcate the anterior and posterior abdominal walls.

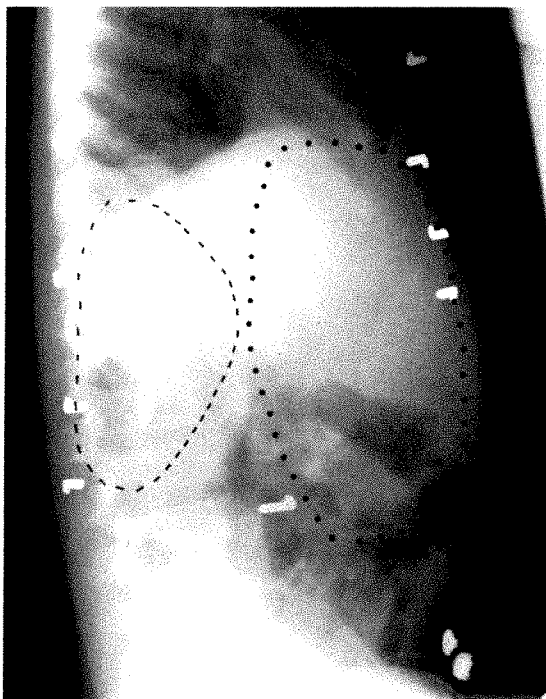


FIG. 5. Superimposition of the liver and renal scans in the right lateral position shows the kidney to lie posterior to the liver. The roentgenogram was obtained at 6 feet from tube to patient. Lead markers correspond to skin marks on the anterior and posterior abdominal wall made at the time of scanning.

chlormerodrin was injected intravenously and a scan was obtained in both the anterior and right lateral positions within 2 hours of injection. The factors for scanning were as before except that a "window" of 55 to 90 kev. was selected to make use of the 77 kev. gamma peak (99 per cent). However, with an amplification factor of 4, the actual settings of the analyzer were 220 and 360, respectively. The maximum count rate was approximately 1,500 per minute.

Superimposition of the liver and renal scan (Fig. 3, 4 and 5) revealed that the right kidney lay behind the liver and was distinct from demonstrable liver tissue. In order to further minimize radiation of the kidney³ while increasing the dose to liver, it was elected to use a single right lateral portal which could be directed to the more anteriorly placed liver and exclude the relatively posterior renal tissue. To still further minimize radiation to the kidney by reducing scatter, a "split beam" was used; 3 mm. of lead was placed in the posterior one-half of the radiation beam (this diminishes the air exposed beam to 1 per cent of the incident

beam) and the central beam was positioned at the posterior edge of the portal.

SUMMARY

In the past, we had attempted to use intravenous pyelography for demonstrating the position of the kidney in this situation. This was not too satisfactory, both because it was difficult to differentiate liver from renal shadows and because of the effect of magnification on the 40 inch intravenous pyelogram compared to portal roentgenograms. It appears that the relatively simple use of radioisotopes to outline these organs in relation to the volume under radiation therapy, without the complication of magnification and with the sharp demarcation possible, would make this a worthwhile procedure.

Department of Radiology
The Children's Hospital Medical Center
300 Longwood Avenue
Boston, Massachusetts 02115

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RADIATION THERAPY IN THE CONTROL OF PERSISTENT THYROID CANCER*

By GLENN E. SHELINE, M.D., MAURICE GALANTE, M.D., and
STUART LINDSAY, M.D.
SAN FRANCISCO, CALIFORNIA

SURGICAL extirpation of the thyroid gland is usually effective in controlling differentiated carcinomas arising in this organ. Local invasion of vital or functionally important structures, however, such as the larynx, trachea, pharynx, and cervical esophagus, may prohibit complete removal of the disease. Such differentiated thyroid carcinoma left in the surgical field frequently causes death by local invasion even though it may progress slowly over a period of several years. Surgical treatment almost uniformly fails with the more undifferentiated forms of thyroid cancer.

The present study was initiated in an endeavor to determine the effectiveness of radiation therapy when treating thyroid malignancy which, because of infiltration into the trachea, larynx, pharynx, or cervical esophagus, could not be completely removed by total thyroidectomy. Some of the lesions which are considered probably could have been resected by supplementing the thyroidectomy with a more radical operation, such as a laryngectomy or pharyngectomy, or both.

The prolonged natural course of many thyroid carcinomas makes it impossible to evaluate in terms of cure a number of patients treated in recent years. Nevertheless reports of these patients are included. They do provide information useful for the evaluation of radiation response, both initially and for periods of time ranging up to many years.

MATERIAL AND TREATMENT

The records of all patients with histologically proved carcinoma of the thyroid seen in the Section of Therapeutic Radio-

TABLE I
PATIENTS REFERRED FOR TREATMENT OF
THYROID CANCER
July, 1935 to June, 1964

Disposition of Patients	No.
Radiation therapy given	
Thyroid area treated:	
postsurgical persistent (44) or	
recurrent cancer (14)	58
without evidence of persistent cancer	30
recurrence after previous radiation therapy	4
Metastases treated	28
No radiation therapy given*	27
Total	147

* Absence of demonstrable disease, or cancer too widespread for radiation therapy.

logy between July, 1935 and June, 1964 were reviewed (Table I). Of a total of 147 such patients, 58 were deemed suitable for the present study. The other 89 were excluded for the following reasons: (a) there was no convincing evidence of persistent local disease at the time of radiation treatment; (b) the lesion treated represented a recurrence of tumor after previous radiation therapy; or (c) no radiation therapy was given to the thyroid area. All cases in which the extrathyroidal extension involved only the overlying strap muscles have been excluded.

The 58 patients included in the study had residual or recurrent extrathyroidal cancer in the surgical field (Table II). In 44 patients surgical excision of the tumor had been attempted but was incomplete because of invasion of the trachea, larynx,

* Presented at the Sixty-sixth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 28-October 1, 1965.

From the Departments of Radiology, Surgery and Pathology, University of California School of Medicine, San Francisco, California.

TABLE II
RADIATION THERAPY TO THYROID AREA FOR PERSISTENT OR RECURRENT CANCER

Histologic Diagnosis	No. of Patients				Total
	Surgical Removal Attempted		Obviously Inoperable		
	Gross Residual ^a	Microscopic Residual ^b	Biopsy Only	Recurrent Cancer ^c	
Papillary carcinoma	7	12	3	5	27
Follicular carcinoma	2	5	—	2	9
Anaplastic carcinoma	2	3	2	—	7
Giant cell carcinoma	3	1	1	—	5
Lymphosarcoma	4	2	—	—	6
Miscellaneous	1	2	1	—	4
Total	19	25	7	7	58

^a Visible cancer incompletely resected.

^b Cancer resected from surface of trachea or other cartilaginous structure.

^c No additional operative procedure attempted.

or esophagus. In 19 of these 44 patients, gross evidence of tumor was present at the completion of the surgical procedure. In the other 25, the diseased tissue was "shaved off" an area of obvious invasion of cartilage or esophageal wall and these patients are presumed to have had "microscopic" persistent disease. Due to obvious involvement of vital structures, no definitive surgical procedure was attempted in the remaining 14 patients.

The tumor was thought to have arisen within the thyroid gland in all patients, regardless of the histologic nature of the malignancy. Although cervical lymph nodes were involved in some with papillary or follicular carcinoma, in no patient in this series was the malignancy demonstrable beyond the cervical region at the time of treatment.

The histologic material was reviewed and reclassified according to the system proposed by Hirabayashi and Lindsay.⁴ Table II shows the number of patients with each histologic type of thyroid cancer. It also indicates the extent of residual tumor present when radiation therapy was begun. Papillary carcinoma occurred in 27 patients; of these gross evidence of residual*

or inoperable tumor was seen in 15 and microscopic persistent tumor was thought to be present in 12. There were 9 patients with follicular carcinoma, 7 with anaplastic carcinoma (including spindle, large, and small cell varieties), 5 with giant cell carcinoma, and 6 with lymphosarcoma. The miscellaneous group included single cases of fibrosarcoma, angiosarcoma, medullary carcinoma, and Hürthle cell carcinoma.

Table III shows a number of clinical features in the patients studied. Tracheal invasion was suspected preoperatively in 8 but was present in 35 of the patients in whom thyroidectomy was performed. It was suspected in 12 of the 14 whose tumors were grossly inoperable and in whom the surgical procedure was limited to biopsy. The neoplastic growth appeared as a mass within the lumen of the trachea or of the hypopharynx in 4 patients with papillary carcinoma.

Paresis of one vocal cord was present preoperatively in 15 patients. Hemoptysis

used to describe tumor seen or felt at completion of the surgical procedure. The term "palpable carcinoma" is used to describe a lesion that was palpable at the time radiation therapy was undertaken. Frequently, gross residual tumor that was obvious at the time of thyroidectomy could not be palpated clinically at the time of radiation therapy. "Microscopic residual" means that during the surgical procedure cancer was resected or "shaved off" the tracheal or thyroid cartilage or the pharyngeal wall; in all probability tumor remained, infiltrating the structure involved.

* In this publication the term "gross residual carcinoma" is

TABLE III
HISTOLOGIC DIAGNOSIS AND COMPOSITION OF SERIES

	Histologic Diagnosis						
	Papillary	Follicular	Anaplastic	Giant Cell	Lymphosarcoma	Miscellaneous	Total
Tracheal invasion suspected/found							
Surgical removal attempted	3/15	0/7	1/4	2/4	0/3	2/2	8/35
Obviously inoperable	6/8	2/2	2/2	1/1	0	1/1	12/14
Preoperative vocal cord paralysis	3	2	3	3	2	2	15
Hemoptysis	3	0	0	0	0	0	3
Previous operative procedure	9	4	0	0	0	0	13
Cancer suspected before surgery	26	6	7	4	3	2	48

was the presenting complaint in 3 of those with papillary carcinoma. Definitive surgical procedures had been performed previously on 9 patients with papillary and 4 with follicular carcinoma.

The techniques of radiation therapy varied according to the gross extent and the histologic nature of the disease, the therapy equipment available, and the radiation

therapist in charge of treatment. The availability of a 1 mev. roentgen-ray therapy machine as early as 1935 made megavoltage irradiation possible in three-fourths of the patients. Radiation doses were calculated in the midplane of the neck or just lateral to it at the sites of presumed residual cancer. These doses ranged from 3,000 r given in 15 days to 6,000 r in 50

TABLE IV
RESPONSE OF PAPILLARY CARCINOMA OF THYROID TO RADIATION THERAPY IN PATIENTS WITH EVIDENCE OF GROSS TUMOR

Sex and Age	Lesion before Therapy			Local Mass after Therapy	Final Result			
					No Local Recurrence		Local Recurrence	
	Gross Residual	Inoperable Recurrence	Palpable		Living (yr.)	Dead (yr.)	Living (yr.)	Dead (yr.)
F 67		X	Yes	Absent	1	—	—	—
M 29		X	Yes	Absent	10	—	—	—
F 52	X		Yes	Smaller	—	25 ^b	—	—
F 50	X ^a		Yes	Absent	—	—	—	7
F 48		X	Yes	Absent	2	—	—	—
M 65	X ^a		Yes	Absent	3	—	—	—
F 63	X		No		14	—	—	—
M 76	X		No		—	—	—	5
F 49		X ^a	Yes	Smaller	2	—	—	—
F 77	X		No		—	6 ^b	—	—
M 61	X		No		—	—	—	18
M 63		X ^a	Yes	Absent	2	—	—	—
M 53	X		No		—	—	5	—
F 65	X		No		5	—	—	—
F 37	X		Yes	Absent	—	1 ^b	—	—

^a Cancer mass present within the tracheal and/or hypopharyngeal lumen.

^b Death unrelated to thyroid cancer.

TABLE V
RESPONSE OF PAPILLARY CARCINOMA OF THYROID TO
RADIATION THERAPY IN PATIENTS WITH EVIDENCE OF
MICROSCOPIC* RESIDUAL CARCINOMA

Sex and Age	Final Result			
	No Local Recurrence		Local Recurrence	
	Living (yr.)	Dead (yr.)	Living (yr.)	Dead (yr.)
F 35	17	—	—	—
F 57	22	—	—	—
F 55	—	6 ^a	—	—
F 17	12	—	—	—
M 23	11	—	—	—
F 35	11	—	—	—
F 68	8 ^b	—	—	—
F 32	6	—	—	—
F 39	6 ^b	—	—	—
F 32	5	—	—	—
F 43	9	—	—	—
M 15	10	—	—	—

* Carcinoma removed from tracheal or laryngeal cartilage by resection or cautery.

^a Died of distant metastases.

^b Metastases have been treated; currently without evidence of cancer.

days. In general, the smaller doses were used for neoplasms such as the lymphosarcomas and the larger doses for the more differentiated forms of carcinoma. In recent years the doses have varied between 5,000 and 6,000 r given in 6 to 7 weeks for the differentiated carcinomas. For the lymphomas they have been somewhat smaller.

RESULTS AND DISCUSSION PAPILLARY CARCINOMA

Table IV gives the results for the 15 patients with papillary carcinoma in whom the tumor was grossly evident after surgical treatment, or in whom there was an inoperable recurrence. In this group, the average age was 57 years; only 2 patients were less than 45 years of age. In the 9 patients with tumor palpable at the time of radiation therapy, the lesion disappeared completely in 7 and decreased in size in the other 2. Cancer had been present within the trachea or hypopharynx prior to radia-

tion therapy in 4 of these 9 patients. Of this group with definite persistent or recurrent carcinoma at the time of radiation therapy, 8 are alive without local recurrence from 1 to 14 years. Deaths of 3 occurred at 1, 6, and 25 years after therapy, of unrelated causes and without local recurrence. One patient is living 5 years after treatment but has a local recurrence and 3 others have died of such recurrence. Initial control by radiation therapy does not necessarily mean a permanent cure. Of the 4 recurrences, 1 was first noted at 1 year, 2 at 5 and 7 years and the fourth at 18 years after treatment. Because of the long natural history of papillary carcinoma of the thyroid, conclusions concerning survival rate cannot be drawn from the present material. This material does indicate, however, that locally persistent papillary carcinoma can be rendered clinically nondetectable and its growth arrested for periods up to 25 years or longer. These findings are consistent with those of Windeyer⁸ who reported marked regression or disappearance of locally inoperable papillary carcinoma of the thyroid in 10 of 24 irradiated patients. Frazell and Foote² presented their results in terms of survival rates rather than of local response. They reported that 10 of 23 patients with inoperable papillary carcinoma survived 5 years or more after radiation therapy. The longest survival in their group at the time of reporting was 26 years.

The 12 patients in whom the papillary carcinoma had been "shaved off" the trachea or thyroid cartilage are listed in Table V. At the time of the surgical procedure, these tumors were noted to be infiltrating into the tracheal or laryngeal cartilage. These patients were generally younger than those with grossly evident residual disease. The average age was 38 years and three-fourths of the group were younger than 45 years. The lower average age in this group may mean that the disease was treated at an earlier stage. Frazell and Foote² made a similar suggestion in a discussion of age and prognosis for

TABLE VI
RESPONSE OF FOLLICULAR CARCINOMA OF THYROID TO RADIATION THERAPY

Sex and Age	Local Lesion before Therapy				Local Mass after Therapy	Final Result			
	Gross Residual	Microscopic* Residual	Inoperable Recurrence	Palp-able		No Local Recurrence		Local Recurrence	
						Living (yr.)	Dead (yr.)	Living (yr.)	Dead (yr.)
F 32	X			No	Same Absent	10	—	—	—
F 11	X			No		16	—	—	—
F 78			X	Yes		—	—	—	3
F 77			X	Yes		2	—	—	—
F 16		X		No		5	—	—	—
M 30		X		No		18	—	—	—
F 28		X		No		—	—	—	4
F 66		X		No		—	—	—	6
F 61		X		No		—	7 ^a	—	—

* Carcinoma removed from tracheal or laryngeal cartilage by resection or cautery.

^a Death unrelated to thyroid cancer.

patients with thyroid cancer. Whatever the reason, this group has done better than the group with gross residual tumor. All 12 patients have been observed for at least 5 years and 6 for 10–22 years. Although 1 patient died from distant metastases, in no instance has local recurrence been demonstrated after radiation therapy. Evaluation of the effect of radiation therapy in this group is difficult, but it seems likely that the therapy has at least delayed, if not prevented, local recurrence. These results lead us to believe that patients with persistent microscopically infiltrating papillary carcinoma should be treated with radiation therapy.

FOLLICULAR CARCINOMA

Follicular carcinoma of the thyroid gland was present in 9 patients (Table VI). In 2 of these, gross residual carcinoma was evident at the time of attempted surgical removal and in 2 others there was an inoperable recurrence. Of these 4 patients, 1 failed to respond to treatment and died 3 years later of local tumor growth. The other 3 are living without recurrence at 2, 10, and 16 years after treatment. Of the 5 patients with infiltration of the trachea but no grossly evident malignant tissue,

2 died of local recurrence approximately 4 and 6 years after treatment, 1 died of an unrelated cause at 7 years, and 2 are living without recurrence at 5 and 18 years.

Thus, of 9 patients with follicular carcinoma, 3 died from the effects of local recurrence and 5 have survived for periods of 5 to 18 years without local recurrence. The ninth patient, although free of local disease, was treated only 2 years ago. Radiation therapy appears to have been effective in controlling tumor growth in some of these patients with follicular carcinoma; however, the results are not as consistently favorable as in papillary carcinoma. The difference in results is particularly striking when consideration is limited to those with only microscopic residual tumor. There was local fatal recurrence in 2 of the 5 such patients with follicular carcinoma but in none of the 12 with the papillary variety. Similar results in the response of papillary and follicular carcinoma to radiation therapy have been reported previously.⁸

ANAPLASTIC CARCINOMA

In 7 patients the thyroid gland contained an anaplastic carcinoma (Table VII). Currently, 1 of these patients is alive and well at approximately 2 years after treatment.

TABLE VII

RESPONSE TO RADIATION THERAPY OF THYROID CANCER OTHER THAN PAPILLARY AND FOLLICULAR

Type	Sex and Age	Local Lesion before Therapy			Local Mass after Therapy	Final Result			
		Gross Residual	Microscopic Residual	Palpable		No Local Recurrence		Local Recurrence	
						Living (yr.)	Dead (yr.)	Living (yr.)	Dead (yr.)
Anaplastic	M 55		X	No	Grew Absent ?	—	6 ^a	—	—
	M 63		X	No		—	—	—	1 mo.
	F 49		X	No		2	—	—	—
	F 68	X		No		—	—	—	3
	F 59	X		Yes		—	—	—	1 mo.
	F 66	X		Yes		—	—	—	7 mo.
	M 56	X		Yes		—	—	—	3 mo.
Giant Cell Carcinoma	F 71		X	No	Grew	—	—	—	1 mo.
	F 43	X		Yes	Grew	—	—	—	2 mo.
	F 51	X		Yes	Grew	—	—	—	2 mo.
	M 72	X		Yes	Grew	—	—	—	1 mo.
	F 64	X		Yes	Grew	—	—	—	1 mo.
Lympho-sarcoma	F 59		X	No	Smaller	17	—	—	—
	F 63		X	No		20	—	—	—
	F 80	X		No		—	3 ^b	—	—
	F 64	X		No		—	—	—	1
	F 75	X		Yes		—	—	—	3 mo.
	F 67	X		No		—	2 ^a	—	—

^a Dead of metastases.^b Death unrelated to thyroid cancer.

One patient died 6 years after treatment as a result of metastases but without local recurrence. The other 5 have died of complications related to recurrence in the thyroid area. Four of the deaths occurred within 7 months from the time of diagnosis. All patients with grossly evident anaplastic carcinoma have died of local recurrence. Radiation therapy was probably beneficial in the 2 patients in whom recurrence did not develop and in the 1 whose recurrence was noted only after 3 years.

GIANT CELL CARCINOMA

Results of treatment in the 5 patients with giant cell carcinoma were uniformly poor. In each the local mass grew perceptibly during the course of therapy and all were dead within 2 months. These results

are comparable to those reported elsewhere for this type of tumor.⁵

LYMPHOSARCOMA

Lymphosarcoma which was thought to have arisen within the thyroid gland and which clinically was confined to the gland at the time of diagnosis occurred in 6 patients. Two of these are alive without evidence of recurrence 17 and 20 years after radiation therapy. A third patient died of cerebral vascular disease 3 years after treatment; lymphosarcoma could not be demonstrated clinically at the time of death. Death resulted from local growth of the disease in the necks of 2 patients and from widespread involvement in 1. The better results in lymphosarcomas compared to those in anaplastic carcinomas are

in accord with the results reported by Walt, Woolner and Black.⁸ Since the prognosis for the lymphosarcomas and the anaplastic carcinomas differ markedly, every effort should be made to distinguish between these two entities.

Although complications of radiation therapy for thyroid malignancy have been described,^{1,3,7} no serious sequelae were observed in the patients of the present study. Disruption of vital structures has not occurred and tracheostomy has not been necessary unless the neoplastic tissue obstructed the airway. Some of these carcinomas appeared more aggressive as the terminal stage of the disease was approached. There was no evidence that such increased aggressiveness was related to the therapy.

Usually, in this Center, inoperable thyroid cancer has been treated with external radiation therapy. Radioiodine therapy has been reserved for situations in which the local lesion and metastases were inoperable and not amenable to external radiation therapy. Radioiodine administered in the quantities required for treatment of thyroid carcinoma provides a total body radiation dose in the order of several hundred rads. Many patients with differentiated carcinomas are in the younger age group and may live for a long time, regardless of the stage of the thyroid cancer. We are concerned, therefore, about such large radiation doses, both because of the possible genetic effects and the possible induction of leukemia. Furthermore, since it is unlikely that a patient can receive more than 1 complete course of radioiodine therapy, withholding of such systemic therapy until the disease is widespread appears logical.

SUMMARY

Between 1935 and 1964, 58 patients received external radiation therapy for local control of thyroid cancer. In each instance the residual cancer tissue was not resected because thyroid cartilage, trachea, or

hypopharynx was invaded. In 33 patients the extrathyroidal extension was grossly evident. In the other 25, there was presumed microscopic involvement of 1 or more of these structures. Patients in whom the extrathyroidal disease was limited to resectable structures, such as the strap muscles or cervical lymph nodes, are not included in the study.

1. Regardless of whether radiation therapy permanently controls a papillary carcinoma of the thyroid, it usually produces a favorable and often long-lasting response. Of the 9 patients given radiation therapy at least 5 years ago for grossly evident papillary carcinoma, 5 have survived 5, 6, 10, 14, and 25 years without recurrence, 1 is living with recurrence at 5 years, and the other 3 have died of recurrence at periods between 5 and 18 years after treatment. All 12 patients with probable microscopic persistent papillary cancer have been observed at least 5 years and 6 have been observed for more than 10 years; none has shown evidence of local recurrence to date.

2. In patients with follicular carcinoma, the long periods of control of several tumors suggest that some do respond to local radiation therapy even though control is less reliable than in the papillary carcinomas. Of the 8 patients with follicular carcinoma treated at least 5 years ago, 6 are without local recurrence. Three of 7 observed 10 years or more are without recurrence at 10, 16, and 18 years after treatment. For patients with locally persistent follicular carcinoma and no evidence of distant spread, local radiation therapy should be attempted before resorting to systemic therapy with radioiodine.

3. Three of the 7 patients with anaplastic carcinoma obtained some benefit from radiation treatment. One was without local recurrence for 6 years, then died of distant metastases. A second patient has been free of disease for 2 years and in a third recurrence developed only after 3 years.

4. All 5 patients with giant cell carcinoma were dead within 2 months.

5. Of 6 patients with lymphosarcoma initially limited to the thyroid, 3 were observed without evidence of the lymphoma locally or elsewhere for periods of 3, 17, and 20 years.

Glenn E. Sheline, M.D.
Department of Radiology
University of California
School of Medicine
San Francisco, California

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RADIATION THERAPY OF CARCINOMA OF THE VOCAL CORD WITHOUT MUCOSAL REACTION*

By JEROME M. VAETH, M.D., and FRANZ BUSCHKE, M.D.

SAN FRANCISCO, CALIFORNIA

IN 1963, we¹ reported the preliminary results in 21 patients with carcinoma of the vocal cord, Stage I and Stage II. These patients were treated between 1958 and 1960 with 1 mev. irradiation to the mid-larynx in doses of 5,500 to 6,000 r in 7 to 8 weeks. Such prolongation of treatment time demonstrated that early mucosal reactions and late complications can be avoided without jeopardizing the curative effect on the tumor. Observation periods of these patients had been reported as from only 14 to 33 months. The following communication complements the earlier one by recording the 5 year results.

STAGE I

Of 9 patients treated, 6 are alive without evidence of active disease or of radiation sequelae 5 years after therapy (Table I). One patient previously reported who had a cordectomy 9 months after irradiation for uncontrolled disease has remained well for 4 years since the operation. Another patient, originally treated for a small lesion of the

middle third of the cord, was free of demonstrable disease on frequent examinations until 2½ years after treatment, when a pin-head size nodule was noted in the posterior third of the same cord. So far, 16 months after cordectomy, the patient is free of disease. The third patient died of a myocardial infarct 28 months after treatment without evidence at necropsy of recurrent tumor.

Important to note is that following such protracted radiation therapy, cordectomy is possible without surgical complications and that laryngectomy in case of radiation failure can be avoided.

Three of the 9 patients with Stage I disease had posterior lesions, all of which were controlled with irradiation. In our experience, the likelihood of control with radiation therapy of early posterior vocal cord lesions is the same as for lesions of the middle and anterior third.

STAGE II

Six of 12 patients treated are without evidence of active disease or radiation

TABLE I
FIVE YEAR RESULTS OF IRRADIATED CARCINOMA CASES OF THE VOCAL CORD

	No. of Patients Treated	Alive 5 Years (controlled)	Died of Intercurrent Disease (carcinoma controlled)	Salvaged Surgically Alive 5 Years (uncontrolled disease)	Died (disease uncontrolled)
Stage I	9	6	1 ^a	2 ^b	0
Stage II	12	6	1 ^c	4 ^d	1 ^e
Total	21	12	2	6	1

* Myocardial infarct. Vocal cord controlled 28 months (necropsy).

^b Cordectomy in 1 patient 9 months postirradiation; in the other 3 years postirradiation.

^c Gastric carcinoma. Vocal cords controlled 44 months (necropsy).

^d Total laryngectomies.

^e Refused laryngectomy.

* Presented at the Forty-seventh Annual Meeting of the American Radium Society, New Orleans, Louisiana, April 8-10, 1965.
From the Section of Therapeutic Radiology, Department of Radiology, University of California School of Medicine, San Francisco, California.

sequelae after radiation therapy. As stated in the previous report, 4 patients with uncontrolled disease had laryngectomies. These patients have remained free of active disease for 5 or more years. One patient who refused laryngectomy died of progressing disease. Another died of carcinoma of the stomach 44 months after radiation therapy of the laryngeal carcinoma, without evidence of active disease at necropsy.

SUMMARY

1. Twenty-one patients with carcinoma of the vocal cord were treated at the University of California Hospital, San Francisco, with 1 mev. irradiation and a protraction of the over-all treatment time of 7 weeks for 5,500 r midline dose or 8 weeks for 6,000 r, an average of 53 days for 6,000 r instead of the previous average protraction of 40 days for 6,000 r (30 per cent). With this greater protraction, morbidity was

markedly reduced; formation of a false membrane and the previously common late edema were not observed.

2. Seven of 9 carcinomas, Stage I, and 7 of 12, Stage II, were controlled.

3. Cordectomy in 2 patients with Stage I uncontrolled or recurrent disease was done in lieu of total laryngectomy, without any surgical complications or recurrent disease to date. In 4 instances of uncontrolled disease in Stage II, laryngectomies were done without ensuing complications.

Department of Radiology
University of California
San Francisco Medical Center
San Francisco, California 94122

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THE ABNORMAL AZYGOGRAM—AN INDEX OF INOPERABILITY*

By DONALD A. WOLFEL, M.D., EUGENE J. LINBERG, M.D., and JOHN P. LIGHT, M.D.
BALTIMORE, MARYLAND

CONTRAST visualization of the azygos venous system is a simple but little publicized radiologic procedure. Our interest in this study at the University of Maryland Hospital was stimulated by the search for a diagnostic examination which might be of value in evaluating the status of the mediastinum in patients with carcinoma of the lung. A practical method of mediastinal lymphography is as yet undiscovered. Alternatively, we turned to azygography in seeking means to detect those patients whose pulmonary neoplasm had extended beyond the limits of resectability.

Azygograms have been performed on 111 patients, 86 of whom had histologically proven primary carcinoma of the lung. These 86 cases will constitute the basis of this report.

Initially, we hoped that the following facets of azygography could be studied: (1) formulation of reliable criteria of an abnormal azygogram; (2) correlation of normal and abnormal azygograms with surgical and clinical findings; and (3) correlation of normal and abnormal azygograms with plain chest roentgenograms. With these parameters in mind, we desired to ascertain: (1) the reliability, if any, of azygography as a clinically useful examination in assessing the mediastinum from a standpoint of determining resectability of a pulmonary neoplasm, and (2) the clinical situation in which azygography would be of maximum diagnostic value.

Other investigations have been reported prior to and after the beginning of this study.^{1,2,3,4,6,7} Most authors agree that false negative (patent vein) studies were relatively frequent, while false positive (blocked vein) studies are rare. Perhaps

one of the better documented series is that of Low, Keyting and Daywitt,² who found only 5 false negative examinations in a series of 54 patients with proven lung cancer. No false positive azygograms were recorded in this study. These authors concluded that the demonstration of a blocked azygos vein is strong evidence of nonresectability.

TECHNIQUE

The technique employed is that which was first described by Tori⁸ and later publicized by Schobinger.⁵ The injection site of choice has been the left tenth rib in the mid-axillary line, employing a 16 gauge marrow needle as the cannulating device. Twenty milliliters of contrast medium (sodium diatrizoate and methylglucamine diatrizoate*) are injected in 3 to 5 seconds and a simple posteroanterior 14 by 17 inch roentgenogram is made at the end of the injection. Only in a few instances has a lateral study been made in order to clarify the findings in the frontal study. Local extravasation of contrast medium into the soft tissues of the chest wall has been an annoying minor problem on occasion. One major complication, a pneumothorax, has been encountered in this series. A number of the patients has been studied on an outpatient basis, without prior sedation.

ANATOMY

The radiologic anatomy of the azygos venous system has been well documented in the past and will not be elaborated upon further (Fig. 1). It is pertinent to point out, however, that, like other authors, we were impressed with the frequent left or midline

* Renovist, Squibb.

* From the Department of Radiology and Division of Thoracic Surgery, University of Maryland, School of Medicine, Baltimore, Maryland.

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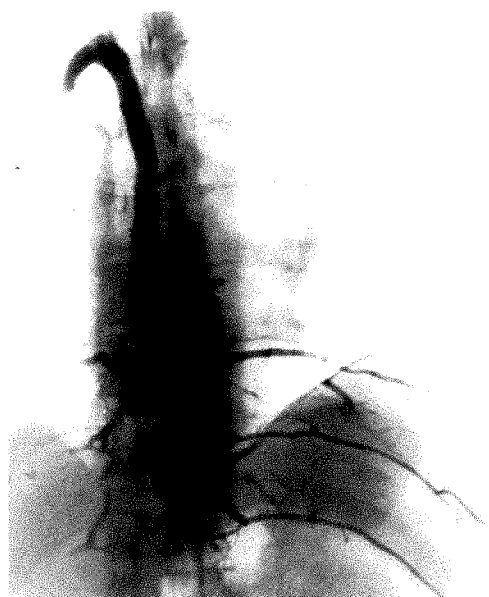


FIG. 1. Normal azygogram.



FIG. 2. Normal azygogram. Note the sweep of the azygos vein to the left of the midline and the normal impression of the right mainstem bronchus. (Procedure performed on right because of technical failure on left.)

position of the azygos vein in the mediastinum, in contradistinction to the usual right position described in standard anatomic texts (Fig. 2). One completely separate uncrossed hemiazygos system was demonstrated, requiring an additional injection into the tenth rib on the right for demonstration of the azygos vein (Fig. 3).

CRITERIA OF ABNORMALITY

A retrospective study of azygograms in the 86 patients with bronchogenic carcinoma led to the establishment of the following radiologic criteria as indicative of an

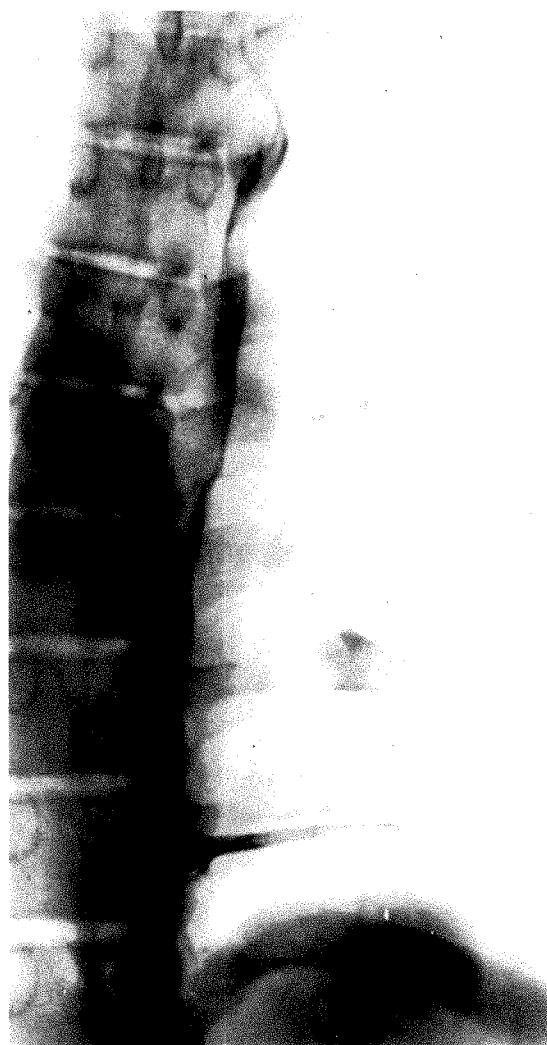


FIG. 3. Anomaly. Completely uncrossed system with filling of only the hemiazygos and accessory hemiazygos by a left-sided injection.

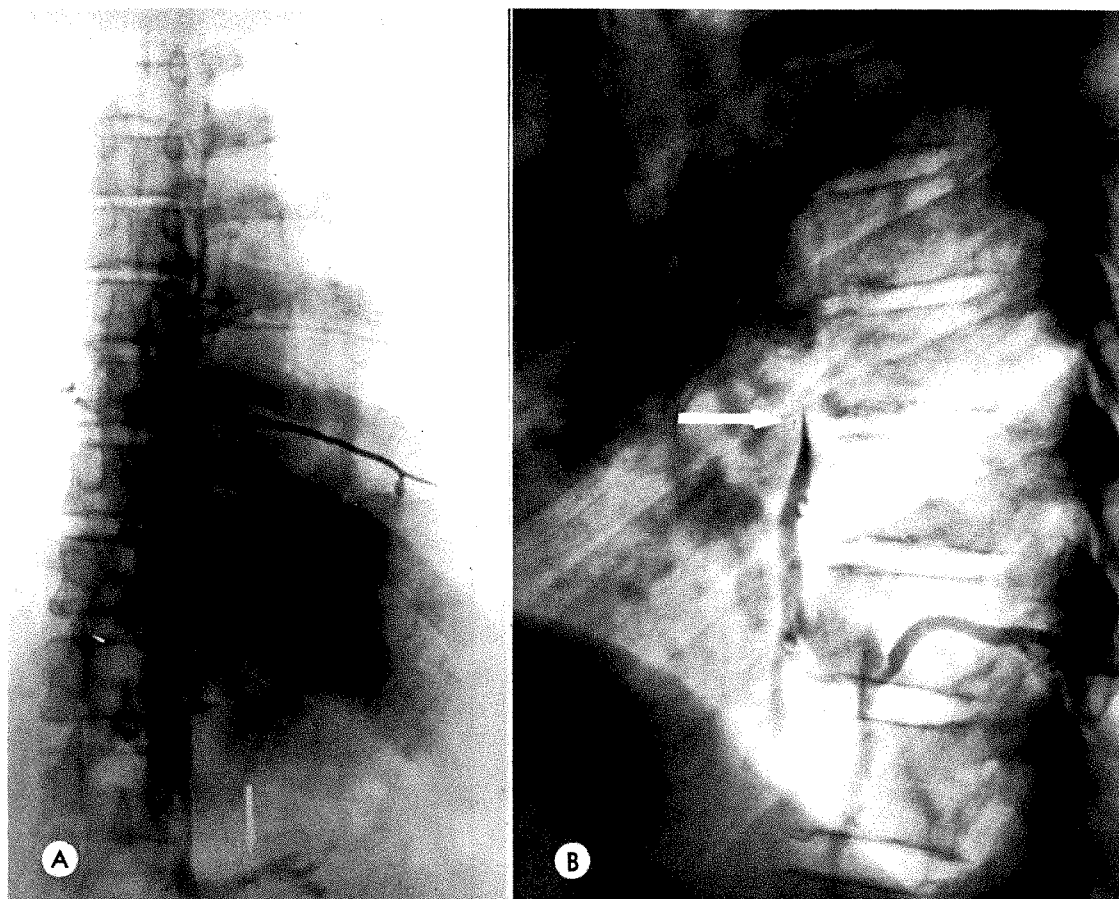


FIG. 4. (A and B) Complete block of the hemiazygos vein at its junction with the azygos. Retrograde filling of the left renal vein is present.

abnormal azygogram: (1) overt block in the azygos venous system (Fig. 4, A and B); (2) failure of opacification of the azygos vein *with* retrograde and/or collateral filling (Fig. 5); and (3) localized venous defect indicating pressure or invasion (Fig. 6). These standards were adhered to as rigidly as possible, although in a few instances interpretation was difficult because of technical factors. The presence of apparent collateral channels associated with an opacified patent azygos vein was seen occasionally; these studies were considered normal.

RESULTS

Eighty-six patients with histologically proven primary lung carcinoma have been studied. For the sake of analysis, they have

been arbitrarily divided into 4 groups, depending upon the status of the azygos venous system and upon whether or not the patients underwent surgical exploration.

Group I consists of 25 patients who had a normal azygogram and who underwent thoracotomy (Table 1). Twenty-one of the 25 were found to have an uninvolved mediastinum at the time of surgery and hence were resectable. Four had mediastinal tumor, either direct extension or metastatic lymph nodes. Three of the 4 false negatives had plain chest roentgen evidence of mediastinal involvement prior to surgery.

Group II consists of 10 patients who had an abnormal azygogram prior to thoracotomy (Table 1). Nine of these 10 patients were found to be unresectable at the time of surgery. The 1 false positive patient un-



FIG. 5. Abnormal study with failure of visualization of the azygos vein and extensive opacification of the vertebral plexus. Some filling of azygos bulb is obtained via collateral veins.



derwent pneumonectomy; the upper lobe tumor was adherent to the lateral chest wall, but the mediastinum was free. The plain chest roentgenogram in each patient in this group indicated hilar and/or mediastinal tumor.

The studies in the group of 35 surgical patients resulted in 4 false negative and 1 false positive azygogram.

In those patients (51) in whom surgery was not performed for a variety of reasons, the efficacy of the azygogram was determined by relating it to clinical and plain roentgenographic evidence of nonresectability. Although it is conceded that such a correlation is subject to inherent error, it is believed that this was kept to a minimum by utilizing overt signs of mediastinal invasion as standards, *i.e.*, carinal fixation, phrenic paralysis, positive scalene lymph node, etc.

Group III is composed of 23 patients who had a normal azygogram (Table II). Correlation in this group was rather poor in that only 11 patients *lacked* clinical and/or roentgen evidence of nonresectability. In

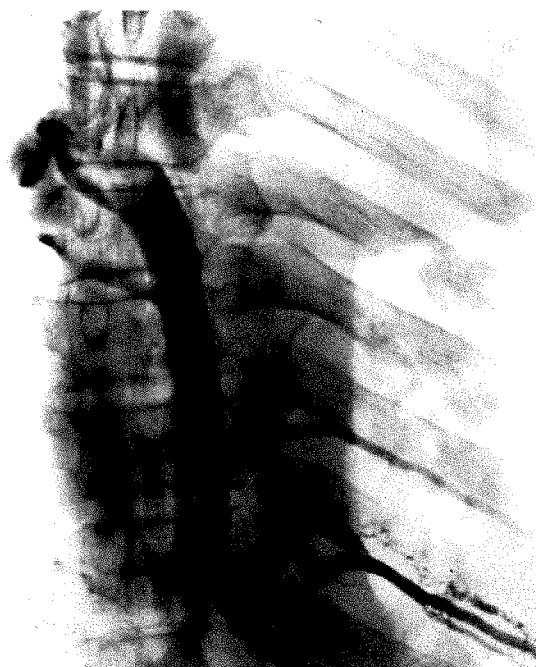


FIG. 6. Direct invasion of azygos arch by tumor, with only low-grade venous obstruction.

TABLE I

GROUP I	
<i>Surgery:</i> Normal azygogram—25 patients	
21/25 resectable	
4/25 mediastinal involvement	
GROUP II	
<i>Surgery:</i> Abnormal azygogram—10 patients	
9/10 nonresectable	
1/10 resectable	
Total surgical patients (Groups I and II):	35
	1 false positive
	4 false negatives

TABLE II

GROUP III	
<i>No Surgery</i> : Normal azygogram—23 patients	
11/23 no clinical or roentgen evidence of nonresectability	
12/23 clinical or roentgen evidence of nonresectability	
GROUP IV	
<i>No Surgery</i> : Abnormal azygogram—28 patients	
28/28 clinical and/or roentgen evidence of nonresectability	
Total nonsurgical patients	
(Groups III and IV):	51
	o false positive
	12 false negatives

10, there was overt roentgen and clinical evidence of mediastinal invasion, while in 2 there were somewhat equivocal findings of the same. All in all, at least 12 false negative studies existed.

Group IV consists of 28 patients who had an abnormal azygogram (Table II). Complete correlation existed within this group in that all patients had plain roentgen or clinical evidence of nonresectability.

Twenty-five patients with miscellaneous inflammatory, neoplastic and undiagnosed intrathoracic processes were also studied (Table III). Of interest are 14 patients with inflammatory lesions, all of whom were explored. Eleven had normal azygograms, the patency of this system ultimately being confirmed at the time of thoracotomy. One

TABLE III

GROUP V	
<i>Miscellaneous</i> —25 patients	
Tuberculosis—4	
*Abscess—2	
Aneurysm—1	
*Granulomatous mediastinitis—1	
*Sarcoidosis—2	
Peripheral granuloma—2	
Fibrothorax—1	
Chronic pneumonia—2	
Carcinoma of esophagus—3	
Metastatic osteosarcoma—1	
Undiagnosed lung lesion, presumed carcinoma—6	

* Block.

patient with a lung abscess and reactive hilar lymphadenopathy, 1 with sarcoidosis and 1 with a granulomatous mediastinitis were found to have an abnormal azygogram, with a complete block in the region of the arch. Thoracotomy confirmed the occlusion of the azygos arch by each of the pathologic processes. Hence, correlation was obtained between azygographic and surgical findings in each of these 14 patients.

The summation of results in this series is shown in Table IV. The excessive number of false negative studies depicts the lack of accuracy of a *normal* azygogram in determining operability. Conversely, the single false positive azygogram reveals the reliability of an *abnormal* study in reflecting inoperability.

TABLE IV
SUMMARY OF GROUPS

<i>Surgery</i> : Normal azygogram	25	} 35	4 false negatives
<i>Surgery</i> : Abnormal azygogram	10		1 false positive
<i>No Surgery</i> : Normal azygogram	23	} 51	12 false negatives
<i>No Surgery</i> : Abnormal azygogram	28		o false positive
Total Proven Carcinoma of Lung	86		
<i>Miscellaneous</i>	25		
Total No. of Patients	111		

SUMMARY

Azygography has been performed on 86 patients with proven bronchogenic carcinoma in an effort to evaluate this procedure in assessing operability of lung cancer. The azygographic findings and the status of the mediastinum have been related surgically in 35 patients and by clinical and plain roentgen evidence in 51 patients. In general, it is fair to say that the azygogram adds little of an informative nature as to the status of the mediastinum than what is already known by clinical or plain roentgen means. In ascertaining resectability, a normal azygogram is of *no* value, while an abnormal azygogram is a strong indication of inoperability. Rather than discard and dismiss this simple roentgenologic procedure, it is believed that it should be applied to that situation in which clinical and/or plain roentgen evidence of mediastinal involvement by a suspected or known pulmonary malignancy is either equivocal or lacking; an abnormal azygogram in such an instance is felt to indicate spread of the malignant process beyond the limits of resectability. As an interesting sidelight, 1 of case of granulomatous mediastinitis, 1 of sarcoidosis and 1 of lung abscess resulting in azygos vein obstruction were discovered

although inflammatory intrathoracic lesions in the main do not alter the azygos venous system.

Donald A. Wolfel, M.D.
Department of Radiology
University of Maryland
School of Medicine
Baltimore, Maryland 21201

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EXPERIMENTAL DETERMINATION OF THE PULMONARY TISSUE FACTOR IN COBALT 60 TELETHERAPY*

By ANTERO VOUTILAINEN, M.D.,† and SOINI VÄHÄTALO, M.A.‡
HELSINKI, FINLAND

IN RADICAL radiotherapy of the lungs, the tissue factor greatly influences the determination of the tumor dose. This factor can be found by: (a) using the general tissue coefficients, such as those published by Wachsmann and Barth;⁶ (b) measuring the incident dose and the exit dose and determining the tissue factor from them, *e.g.*, according to Wachsmann⁵ or Plesch;⁴ and (c) measuring the thickness of non-water equivalent tissue and determining the tissue factor from tables or curves of the type published by Dahl and Vikterlöf,² Keller and Haubold,³ and Burlin.¹

Another method of finding the pulmonary tissue factor is to measure the dose of radiation in the field of irradiation at the esophagus and to determine from this the correction coefficient for the assessment of the correct tumor dose. This method was used in a group of 9 patients, reported in the present paper, the source of radiation being Gammatron 1 Co⁶⁰.

METHOD

Sievert chambers, measuring 5×20 mm., were placed in a plastic tube according to the scheme shown in Figure 1. The chambers were separated by two small rubber balls, between which there was a piece of brass to indicate the position of the chambers on the roentgenograms. The plastic tube was inserted into the patient's esophagus so that the chambers were within the irradiated field. The focus-skin distance was 60 cm. Eight patients had only 1 stationary field over the thorax (Fig. 8B) while 1 patient had 3 stationary fields (Fig. 9B). The dose given for the measurements was 200–250 rads.

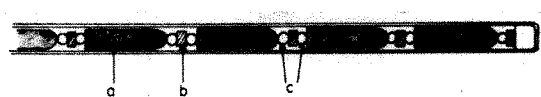


FIG. 1. Sketch of Sievert chambers in the plastic tube. a=measuring chamber, b=brass piece, c=rubber balls.

Table 1 shows the measurements obtained in the 9 cases. The size of the field of irradiation (a) on the skin and (b) at the point of measurement is indicated. The table also shows the dose as a percentage of the field dose at the depth of measurement without the tissue factor in a water phantom, and the corresponding percentage of the measured *in vivo* dose. The tissue factor coefficient was calculated from a comparison of these two percentages. Furthermore, the table gives the thickness of the lung at the point irradiated, *i.e.*, the point at which the tissue factor coefficient is required. The graph in Figure 2 was obtained in this way; it shows the pulmonary tissue factor as a function of the thickness of the part of lung to be irradiated.

RESULTS AND CONCLUSIONS

The distribution of the dose at the point of measurement in the patient's axial direction is shown for each of the cases in Figures 3, 4 and 5. The curves reveal that the doses on the cranial side are usually greater than those on the caudal side of the field. Curves 4 and 6 are exceptions; however, follow-up study in Case 4 showed that the measuring chambers had been placed slightly to one side of the radiation beam; resulting in a measured dose which was considerably smaller (Fig. 6). In Case 6 (Fig. 4, curve 6) a *solid* tumor was present in the right upper

* From the Department of Radiotherapy, University Central Hospital, Helsinki, Finland.

† Department of Radiotherapy, Professor of Radiotherapy, Turku University.

‡ Department of Radiotherapy, Assistant Physicist, Helsinki.

TABLE I
PERCENTAGE DEPTH DOSE IN WATER PHANTOM AND AT THE POINT OF MEASUREMENT AND
THE CALCULATED TISSUE FACTOR

Case No.	Diagnosis	Field Size (cm.) (a) on the skin (b) at the point of measurement	Percentage Depth Dose		Tissue Factor	Thickness of Lung at Point Corresponding to Tissue Factor (cm.)	Remarks
			Water Phantom	<i>In Vivo</i>			
1	Pulmonary cancer	(a) 10×10 (b) 12.5×12.5	36.5	42	1.15	8	
2	Mediastinal tumor with pleural metastases	(a) 8×10 (b) 10×12.5	36	35	1.0	5	
3	Pulmonary cancer	(a) 8×8 (b) 9.7×9.7	42	49	1.17	8.5	
4	Pulmonary cancer	(a) 8×10 (b) 9.7×12.1	41	35	—	8	The radiation beam has partly passed through the measuring chambers
5	Pulmonary cancer	(a) 8×10 (b) 10.6×13.2	25	29	1.16	8	
6	Pulmonary cancer	(a) 10×15 (b) 12.2×18.3	41 41	42 53	1.02 1.29	5 11	A solid tumor, the size of an egg, in the right hilus
7	Pulmonary cancer	(a) 10×12 (b) 12.7×15.2	34	43	1.26	10	Ring-like shadow in the left hilus
8	Pulmonary cancer	(a) 8×15 (b) 10.0×18.7	37	36	1.0	—	Lung filled with fluid
9	Pulmonary cancer	3 fields, Fig. 9, A and B	123	150	1.22		Only 2 beams of radiation have passed through the lung

hilus, located in front of the object of measurement (Fig. 7A). It is evident that the tumor was responsible for the diminished dose at that point (42–43 per cent) in the cranial area of the field, since the dose

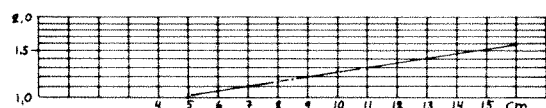


FIG. 2. Pulmonary tissue factor as a function of thickness.

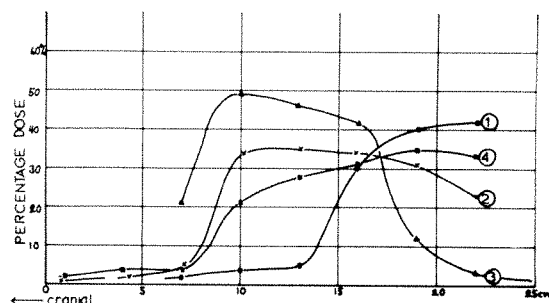


FIG. 3. Distribution of dose in axial direction at the point of measurement in Cases 1 through 4.

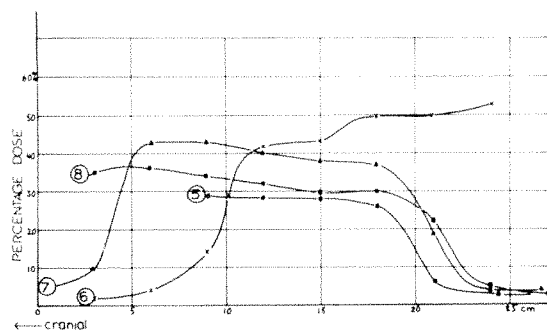


FIG. 4. Distribution of dose in axial direction at the point of measurement in Cases 5 through 8.

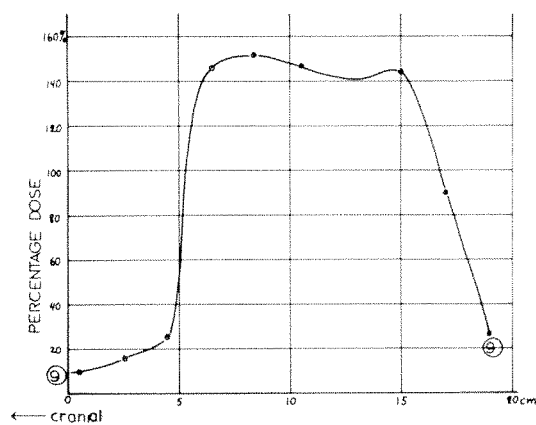


FIG. 5. Distribution of dose at the point of measurement in Case 9, where 3 stationary fields were employed.



B

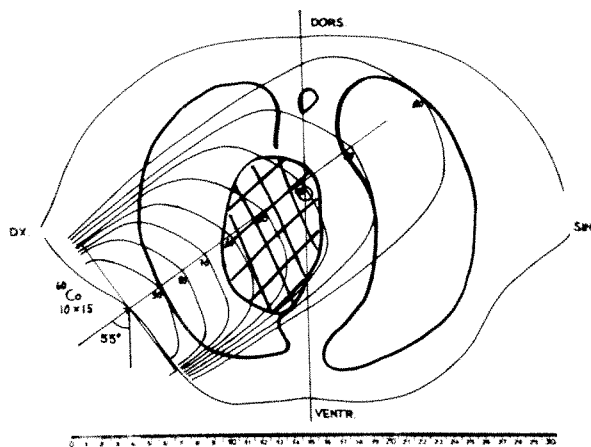


FIG. 7. (A) Anterior view of lungs showing a *solid* tumor in the right hilus in front of the point of measurement. (B) Calculated dose distribution in the tumor (shaded area) and the point of measurement (41 per cent).

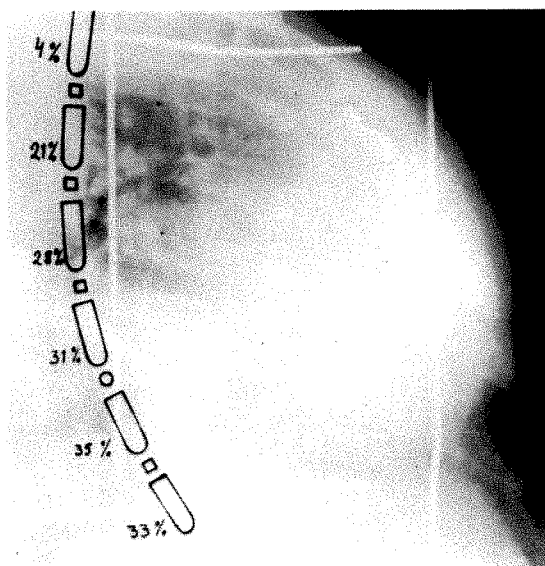


FIG. 6. Lateral view of the points of measurement; the measuring chambers are found to lie outside the beam of radiation. Distribution of dose at different points is shown.

was 49–53 per cent at a point measured outside the tumor in the caudal area of the field where pulmonary tissue alone was in the radiation field (Table 1, Case 6). In Case 1 (Fig. 3, curve 1) only part of the field was measured, since the lowest measuring chamber extended only to the center

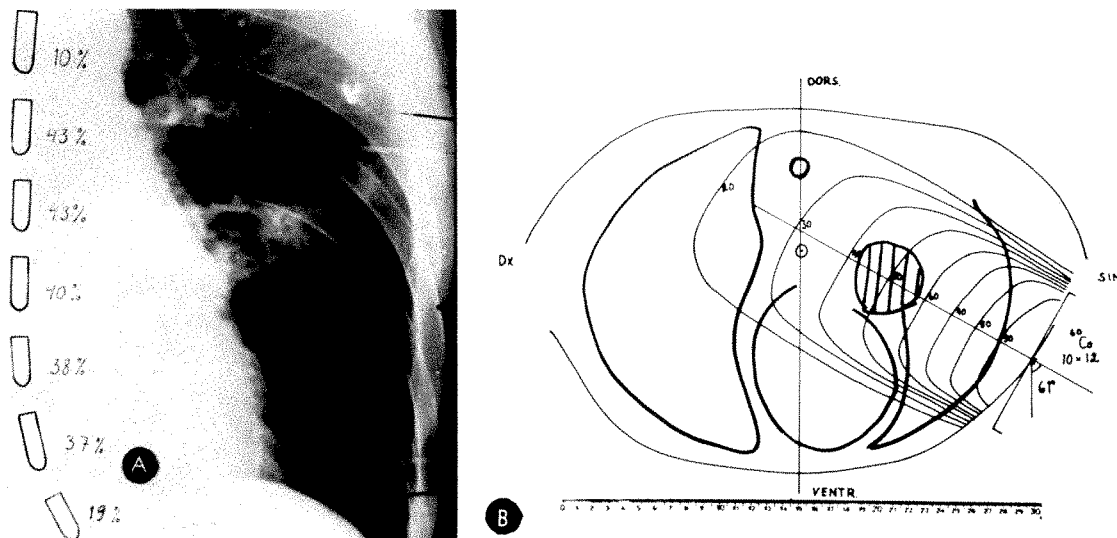


FIG. 8. (A) Anterior view of lungs showing a ring-like *soft* shadow in the left hilus. (B) Dose distribution calculated for the tumor (shaded area) and the point of measurement.

of the tumor, where the measured dose was 42 per cent. In Case 7 (Fig. 8A) a roentgenogram demonstrated a *soft* ring-like shadow in the left hilus and not a solid tumor. Here, the dose diminished caudad in the field of irradiation from 43 to 37 per cent, since in the caudal area the radiation beam falls on the heart and the proportion of the lung is reduced (Fig. 8, A and B). Curve 7 (Fig. 4) shows that the ring-like shadow did not produce a dose reduction due to the fact that it gradually decreased in density caudad.

Although the present series is small the resulting curves expressing the tissue factor (Fig. 2) agree with those obtained on the basis of Dahl-Vikterlöf's measurements, and, therefore, in spite of the small number of cases, they may be considered reliable. According to the measurements, the caudal area may receive a dose of radiation 10–15 per cent smaller than the cranial area, since the patient's thickness increases caudad and the depth of irradiation is greater (Fig. 3, 4 and 5). This, of course, varies with the individual. Craniad, on the other hand, the thickness is reduced, but so is the thickness of the lungs, thus the tissue factor is also reduced and the dose diminished. These phenomena, in part, cancel each other's effect.

The measurements agree with the ones made in phantoms, if the tissue factor is being used, provided the measuring chambers are in the field of irradiation and there is no solid tumor in front of the point of measurement.

The pulmonary tissue factor must be assessed for the exact lung thickness and the solidity of the tumor must be estimated from roentgenograms. If a solid tumor is obviously present (Fig. 7A), it must be considered to be at least water-equivalent, and the pulmonary tissue factor must be assessed for the thickness of the unaffected lung. Should the roentgenogram show a relatively soft shadow of the tumor (Fig. 8A), it should then be considered as approximating the consistency of pulmonary tissue and be included in the determination of the tissue factor. In other words, to determine the correct depth dose, the consistency of the tumor must be assessed from roentgenograms, but if there is fluid in the field of radiation it must be calculated as water-equivalent, and, therefore, reducing pulmonary tissue. As a result the tissue factor also diminishes.

Figure 9 B shows the results of measurement obtained in Case 9 for 3 stationary fields, and the position of the fields. It should be noted that only 2 beams of radi-

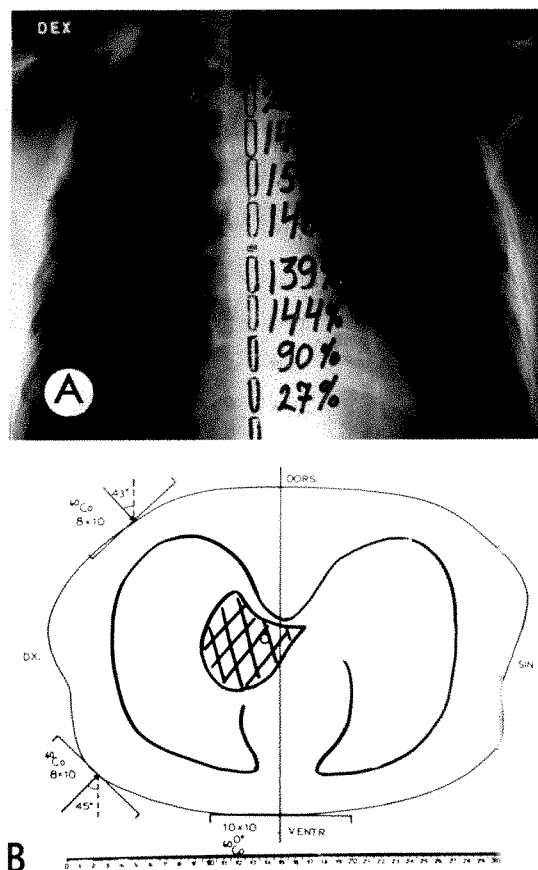


FIG. 9. (A) Distribution of dose at the point of measurement when 3 stationary fields are employed; only 2 beams of radiation have passed through the lung. (B) Treatment plan with 3 stationary fields and the beam of radiation passing through the lung in 2 directions.

tion have passed through the lung. The tissue factor in this case is 1.22 when the measurements (Fig. 5, curve 9) are compared to those obtained by using a water phantom.

According to the measurements, the depth dose immediately outside the field of radiation falls below 10 per cent. This is why the beam of radiation must, of necessity, be directed towards the tumor, the position of which must be checked on roentgenograms. The thorax usually gets wider in the caudal direction; thus the depth dose diminishes with increasing distance and the

tumor receives no homogeneous irradiation—a fact which must be taken into account when therapy is planned. Correction can be achieved by wedge filters.

SUMMARY

To determine the pulmonary tissue factor in cobalt 60 teletherapy, the dose of radiation was measured *in vivo* within the field of radiation by introducing Sievert chambers into the patient's esophagus. At the same time, the dose received as determined from a water phantom at the same depth was also measured. By comparing these results, the tissue factor was calculated. The result obtained agreed with those employing other types of measurements.

It was also found that the doses delivered craniad over the thorax are larger than those delivered caudad, due to the fact that the thoracic thickness decreases craniad. The pulmonary tissue factor also depends on the consistency of the tumor in the lung.

Prof. Antero Voutilainen
Mäntykallio A5
Matinkylä, Finland

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REMOTE VAGINAL METASTASES FROM CARCINOMA OF THE COLON*

By LOUIS RAIDER, M.D.

MOBILE, ALABAMA

VAGINAL metastases from carcinoma of the colon, other than those extending directly into the vagina from the rectum or rectosigmoid, are extremely rare. The observation of 4 such cases, 3 of which were seen within a 15 month period in the Radiation Therapy Department of Providence Hospital, was felt worthy of report and is the basis of this paper. A review of the literature, presentation of cases and discussion of the significance of the finding are included.

The vaginal lesions in all 4 of our patients were manifest as remote metastases discovered at intervals varying from 4 to 41 months following resection of the primary colonic lesion (Fig. 1; and 2, *A* and *B*). None showed any continuity with the colonic lesions and in only 1 (Case II) was there evidence of recurrence of carcinoma in the colon.

A review of the literature reveals a remarkable dearth of reported material on this subject. The only similar case is reported by Whitelaw *et al.*¹² in a woman who had a vaginal lesion which proved to be adenocarcinoma. Three months later, at the suggestion of the pathologist, the gastrointestinal tract was investigated and carcinoma of the mid-sigmoid was found and resected. All other reports in an extensive review of the literature have concerned vaginal involvement by direct extension through the posterior vaginal wall from carcinoma of the rectum or rectosigmoid.

A review of textbooks of pathology, gynecology and cancer revealed only 2 in which the gastrointestinal tract was mentioned as a source of metastatic disease in the vagina. One of these books is "Gynecology" by Parsons and Sommers;¹⁰ the other is "Gynecologic and Obstetric Pathology" by Novak and Woodruff.⁹

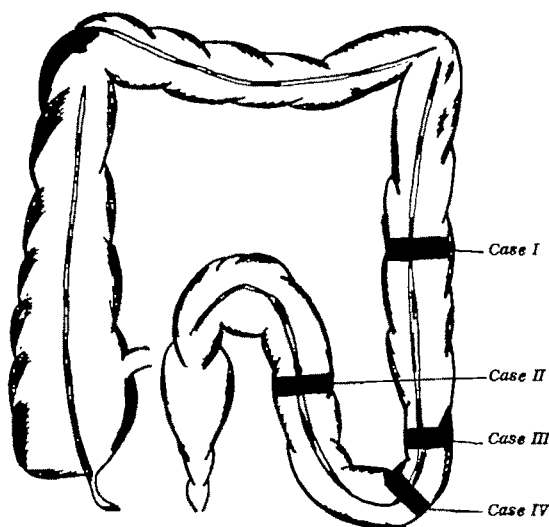


FIG. 1. Locations of primary tumors in the colon.

If we exclude metastases from carcinoma of the cervix, the 4 cases of metastatic lesions from the colon developed among 9 cases of metastatic vaginal lesions seen in our department since 1950. Two of the latter were from the uterine fundus and 3 were from the ovary. Since 1950, we have also seen and treated 10 patients with primary vaginal carcinoma, 1 with a vaginal sarcoma, 350 patients with carcinoma of the cervix and 75 patients with carcinoma of the fundus of the uterus.

REPORT OF CASES

CASE I. I.M.H. was seen at the age of 47 in May of 1955 with a metastatic vaginal lesion, 1.0 cm. in diameter, in the posterior vaginal fornix which had been reported as adenocarcinoma metastatic from the colon (Fig. 3*B*). Thirteen months earlier she had undergone a left colectomy for an annular obstructing carcinoma of the mid-descending colon (Fig. 3*A*). Since, when we saw her for her metastasis, there was no evidence of neoplasm elsewhere, the vaginal lesion was treated as one would treat

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a carcinoma of the cervix. Radium was used with a uterine dose of 3,165 mg. hr. and a vaginal dose of 3,963 mg. hr. with a total dose of 7,128 mg. hr. It was felt that this type of radiation, in addition to treating the local lesion, would encompass other areas of potential metastases.

At laparotomy 3 months later, the pelvis was free of neoplasm. There was, however, studding of the peritoneum in the upper abdominal area with numerous nodules of metastatic neoplasm averaging 0.2 cm. in diameter. At the brim of the pelvis a lymph node, approximately 2.0 cm. in diameter, was resected. This was confirmed as metastasis from carcinoma of the colon.

Because of the radiosensitivity of this patient's tumor, additional radiation therapy was administered. Between May 23, 1955 and July 19, 1955, 2,000 r in air was delivered to 4 anterior and 4 posterior abdominal portals, each measuring 12 by 15 cm., using the following factors: 250 kv., half value layer 1.45 mm. Cu,

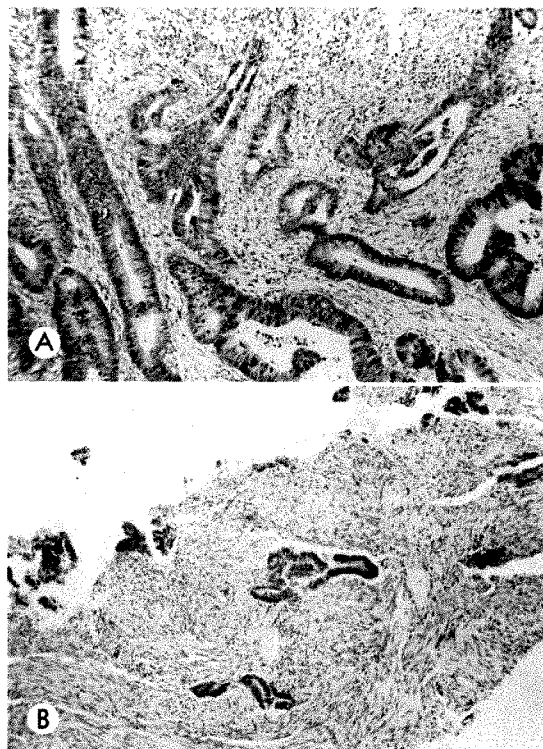


FIG. 3. Case I. (A) Primary colonic lesion. (B) Metastatic vaginal lesion.

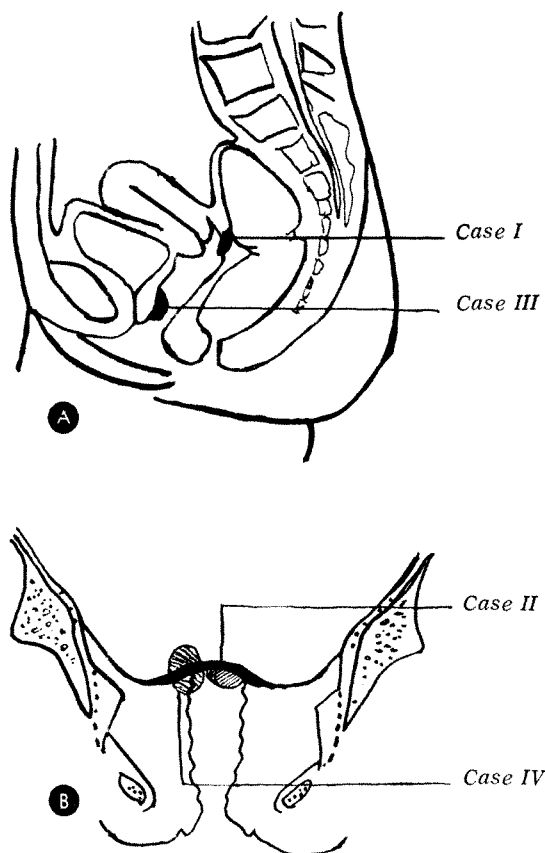


FIG. 2. (A and B) Locations of metastatic vaginal lesions.

and 50 cm. target skin distance. The response was good and there was no evidence of tumor in the vagina or abdominal area for an interval of more than 2 years. She returned to work as a clerk in our department.

In August of 1957, progressively severe cerebral symptoms occurred. Ventriculography revealed a large right occipital mass which was resected and reported as metastatic adenocarcinoma, secondary to the patient's colonic lesion. A course of radiation therapy was administered to the cerebral area with considerable improvement. In March of 1958, symptoms recurred and the patient went steadily downhill, dying on April 17, 1958, 52 months after resection of the colonic lesion and 39 months following identification of the vaginal metastasis.

Comment. The primary lesion in this patient was the most distant from the vagina and was in the mid-descending colon. The metastatic vaginal lesion was controlled permanently. The tumor, despite its colonic origin, was radiosensitive and the vaginal, abdominal and cerebral metastases showed

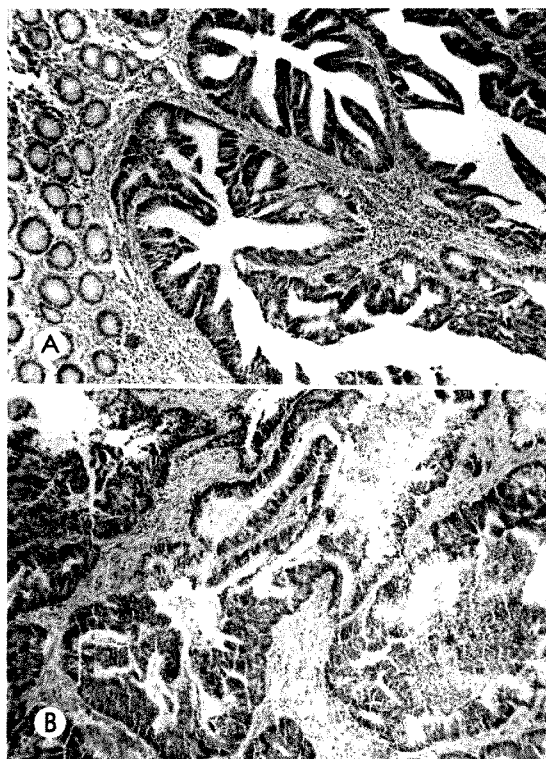


FIG. 4. Case II. (A) Primary colonic lesion. (B) Metastatic vaginal lesion.

excellent response. The extent and distribution of the metastases are a good example of venous spread from the colon.

CASE II. E.S.O. was a 48 year old white woman who on March 7, 1961 had had a left colectomy and total hysterectomy for an obstructing carcinoma of the proximal sigmoid with bilateral ovarian metastases. The annular lesion was 5.0 cm. long and showed evidence of extension through the bowel wall as well as involvement of the lymphatics and regional lymph nodes (Fig. 4A). Palliative radiation therapy was administered with a cobalt 60 unit delivering a dose of 2,000 r to the upper abdominal area and 2,400 r to the pelvis.

On July 11, 1961, vaginal examination revealed a nodular mass in the vaginal vault, measuring approximately 3.5 cm. in diameter, which proved to be metastatic adenocarcinoma from the colon (Fig. 4B). Vaginal radium was applied by means of a Kaplan colpostat and cork, and between July 17, 1961 and July 22, 1961 a dose of 4,130 mg. hr. was delivered. The vaginal lesion disappeared and there was no evi-

dence of recurrence at the time of the patient's death. In February of 1963, she was re-admitted to the hospital because of recurrent obstruction by neoplasm in the sigmoid and evidence of extensive intra-abdominal metastases including hepatic involvement. She went steadily downhill and expired on April 20, 1963.

Comment. This patient had disseminated disease when first explored. The vaginal lesion was discovered 4 months after resection of the colonic lesion and she survived 25 months following resection of the primary lesion and 21 months following the discovery of the vaginal metastasis. She is the only patient in the series who had recurrence in the colon.

CASE III. M.A.E. was a 63 year old white woman who had had a left colectomy in April, 1960 for an obstructing carcinoma at the junction of the descending colon and sigmoid. The lesion was annular and ulcerating and was classified as Grade II with lymphatic invasion (Fig. 5A). The postoperative course was un-

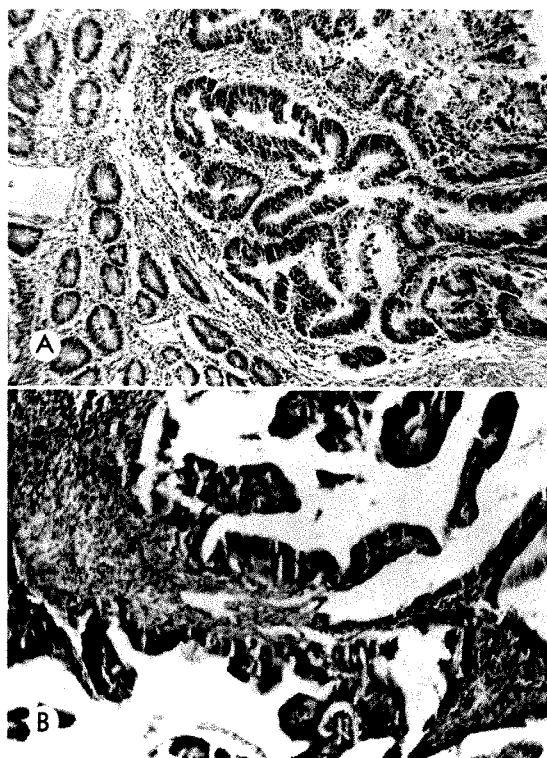


FIG. 5. Case III. (A) Primary colonic lesion. (B) Metastatic vaginal lesion.

eventful until January, 1962, when vaginal bleeding led to the discovery and subsequent resection of a metastatic lesion of the anterior vagina just behind the pubic arch (Fig. 5B). At this time she received a course of nitrogen mustard.

The vaginal lesion recurred as a 4.0 cm. nodule in May, 1962, and the patient was referred to us for radiation therapy. She was treated by a combination of cobalt 60 and radium mold therapy and a dose of 7,000 r was delivered to the tumor. The mass disappeared and the patient was well until November, 1963, when she developed a fecal fistula through the vagina. Injection of the fistula showed small bowel communication; a 20 cm. segment of ileum was resected along with the fistula and a primary anastomosis was done. During this operation, a careful examination of the entire abdominal cavity revealed no evidence of neoplasm. The postoperative course has been uneventful and the patient has gained 30 pounds. She is now well without evidence of neoplasm 4 years after the discovery of the vaginal metastasis and 6 years following resection of the primary colonic lesion.

Comment. This case is unusual in many respects. The metastatic lesion appeared 21 months after resection of the primary colonic lesion. She is alive and well 48 months after the discovery of the metastatic lesion with no evidence of disease. The occurrence of a fistula permitted a second look into the abdomen, at which time there was no evidence of neoplasm in the liver, peritoneum or pelvis. It is hoped that she may be one of the rare individuals with isolated distant metastasis, the control of which will permit long time survival*

CASE IV. E.U. was seen for a check-up in September, 1962, at which time a 5.0 cm. mass was palpated in the vault of the vagina. This mass was continuous with neoplasm in the cul-de-sac. Biopsy revealed adenocarcinoma metastatic from the colon (Fig. 6B). Forty-one months earlier in February of 1959, she had undergone resection of an obstructing carcinoma of the proximal sigmoid (Fig. 6A). Two years later in January, 1961, a second laparotomy had been done for a pelvic mass which

* At the time of publication of this paper, the patient was still alive and well with no evidence of disease.

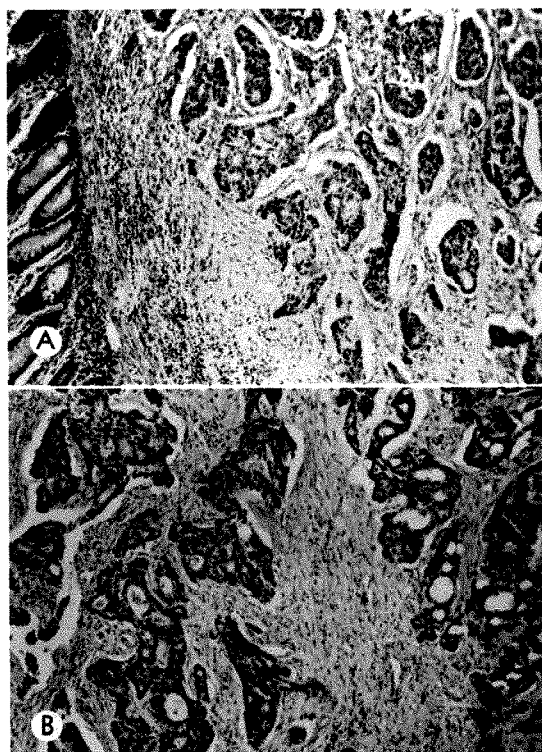


FIG. 6. Case IV. (A) Primary colonic lesion. (B) Metastatic vaginal lesion.

was identified as ovarian metastasis from colon. Between February 8, 1961 and April 25, 1961, 1,900 r in air was delivered through two anterior and two posterior 16 by 20 cm. abdominal and pelvic portals, using the following factors: 250 kv., half value layer 1.45 mm. Cu, and 70 cm. target skin distance.

The vaginal lesion was treated with radium and a dose of 3,605 mg. hr. was delivered through a Kaplan colpostat and cork. This was followed by a course of cobalt 60 teletherapy, delivering 3,200 r to the pelvis. Radiation therapy was completed on January 28, 1963. There was regression but not complete disappearance of the vaginal tumor. The patient's liver became palpable and pulmonary and mediastinal metastases were noted. She went gradually downhill and expired with generalized carcinomatosis on July 15, 1963.

Comment. This case had the longest interval between resection of the primary carcinoma and the appearance of vaginal metastasis. The vaginal lesion appeared 41 months following resection of the colonic carcinoma. She survived only 10 months

TABLE I

Case	Age (yr.)	Primary Colonic Location	Metastatic Vaginal Location	Interval between Colonic and Vaginal Lesion (mo.)	Survival Time following Vaginal Lesion (mo.)	Vaginal Lesion Controlled	Recur-rence in Colon	Classification of Primary Carcinoma	Other Metastases
I I.M.H.	47	Mid-Descending	Posterior Fornix Left	13	39	+	○	Grade III Dukes B Annular	Brain Omentum Peritoneum
II E.O.	48	Mid-Sigmoid	Vaginal Vault	4	21	+	+	Grade II Dukes C Annular	Ovaries Uterus Pleura, Liver
III M.A.E.	63	Distal Descending Junction with Sigmoid	Introitus Left	21	48 (alive and well)	+	○	Grade II Dukes C Annular	
IV E.V.	46	Proximal Sigmoid Junction with Descending	Vault Left	41	10	—	○	Grade II Dukes C Annular	Ovary Ileum Peritoneum Mediastinum

after the discovery of the vaginal metastasis, for a total of 51 months. The tumor was less radiosensitive than that of the others and was not controlled by radiation therapy. The vaginal lesion in this patient appeared to be continuous with an implant in the cul-de-sac.

DISCUSSION

The pertinent data of the 4 patients included in this report are summarized in Table 1. In 3 of these patients, the vaginal metastasis was part of widespread dissemination of carcinoma of the colon. The fourth (Case III) showed only the isolated vaginal lesion and it is hoped that she will be one of those rare cases with a single isolated metastatic focus which will permit long time survival.

Speculation regarding the mechanism of spread of carcinoma from colon to a remote site in the vagina is interesting. The subject has been admirably covered by several authors including Grinnell,⁶ Whitelaw *et al.*¹² and Dockerty.⁴ Colonic neoplasm may spread by: (1) direct extension; (2) implantation; (3) lymphatic channels; and (4) venous plexuses.

It is possible for carcinoma to spread from the colon to the vagina by lymphatic

routes. This would include spread through lymphatics from the sigmoid to the iliac and hypogastric lymph nodes. There would then be further retrograde spread through the lymphatics from the iliac and hypogastric lymph nodes to the peri-urethral area and the anterior vaginal wall. Only 1 of our patients (Case III) had a lesion adjacent to the urethra and, at exploration for closure of the fistula, no evidence of involvement of iliac or hypogastric lymph nodes was identified.

The most likely pathway of spread from the colon to the vagina appears to be via the venous channels, particularly by the vessels associated with the vertebral vein system. Through these vessels, tumor emboli may pass from the primary site in the colon to the ovarian plexus or parametrial veins and from these to the vaginal veins where the emboli will be borne to the vagina or vulva. This was excellently described by Batson,¹ from whom we quote: "the vertebral vein system consists of the epidural veins, the perivertebral veins, the veins of the thoraco-abdominal wall, the veins of the head and the veins of the walls of the blood vessels of the extremities. It is a set of valveless vessels that carries blood under low pressure. In the subcutaneous

tissue the smaller vessels provide a continuous network permitting ready permeation. Around the vertebral column the vascular bed of the system is so much larger than required by the parts in which it is found. It is a system which is constantly subject to arrests and reversals in the direction of flow of blood. The vertebral vein system parallels, connects and provides bypasses for the portal, the pulmonary and caval systems of veins and hence can provide in itself a pathway for the spread of disease between remote organs."

In 3 of our patients (Cases I, II and III) spread seemed to be from the colon to the vagina by the venous route. In the fourth case (Case IV) it appeared to have reached the vagina by a combination of implantation to the peritoneum in the cul-de-sac and then by extension from this implant through the vaginal wall into the vagina.

There is a definite correlation between the degree of annularity of a colonic carcinoma and remote spread. Annular lesions are older than those which circumscribe only a portion of the bowel and, therefore, are more apt to spread through the lymphatics and veins. It should be noted that all of our patients had annular obstructing lesions.

Other writers have also reported a correlation between the grade of tumor and remote metastases, reporting more frequent remote metastases with Grade III and Grade IV lesions. It is interesting to note that only 1 of our patients was classified as Grade III and that the other 3 patients were classified as Grade II.

It seems unlikely that vaginal metastases from carcinoma of the colon are as rare as a review of the literature might indicate. It should be noted that only 1 of our patients had any symptomatology referable to the vagina (Case III) and that the other metastatic lesions were discovered during routine check-up of the patient which included vaginal examination and speculum inspection. It is probable that if all patients who have had carcinoma of the colon and, particularly, those who have other evidence of

spread are examined thoroughly a greater incidence of vaginal metastasis may be reported. Certainly, based on our experience and that of other authors, unexplained adenocarcinoma in the vagina should call for a thorough investigation of the gastrointestinal tract.

The prognosis when one finds a vaginal metastasis from carcinoma of the colon is ominous. It usually heralds widely disseminated neoplasm and impending death. The prognosis is, however, not completely hopeless for occasionally, as with pulmonary and hepatic metastasis, the lesion is solitary and its resection may be compatible with long survival.

Therapy was directed toward eradicating the neoplasm and as much of the adjacent tumor bearing tissue was included as possible. By the use of combined intracavitary and external irradiation, the vaginal lesion was controlled in 3 of our patients, while some palliation was accomplished in the fourth.

SUMMARY

Four cases of remote and late metastases to the vagina from carcinoma of the colon are reported.

The incidence, diagnosis, treatment, routes of spread and prognostic implications are discussed.

1720 Spring Hill Avenue
Mobile, Alabama

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PREGNANCY FOLLOWING OVARIAN IRRADIATION*

By MARIO M. VUKSANOVIC, M.D.

MIAMI, FLORIDA

A GREAT amount of literature has been reviewed concerning both morphologic and functional effects resulting from the exposure of the ovaries of women in the reproductive age to ionizing radiation. Frequently, this exposure has come about during the process of administering some form of radiation therapy to malignant tumors of the genital tract. In some instances, younger patients with cancer of the breast have had their ovaries irradiated during the course of therapy of their disease; however, more often, the reports concern ovarian irradiation in women approaching the climacterium for the purpose of controlling disorders of varied nature.

There is an obvious lack of precise information despite this ample material as to the quantitative and sequential events taking place in the irradiated human ovaries.¹² Among the reasons usually advanced for this lack of precise knowledge are: the various kinds of radiant energy utilized; the manifold dose rates and different techniques of irradiation; and, not infrequently, the incomplete data of the reporters. Conversely, the strictly controlled studies on inbred strains of laboratory animals are not applicable to the clinical situation. Consequently, there is a wide discordance in reported studies as to the optimal radiation technique to be used when one wishes to permanently arrest the oogenesis in patients of a reproductive age.⁷

The ovaries, during the administration of radiation therapy for control, in a fertile woman, of invasive carcinoma of the uterine cervix, are customarily irradiated to such a degree that there is an irreversible morphologic and functional alteration. Therefore, subsequent menstruation and ovulation are no longer possible. The aforementioned studies have been convincingly substantiated by biochemical assays and morpho-

logic studies of the ovaries of the irradiated patients subsequently operated upon.^{1,2}

Only rarely have reports appeared specifically describing successful pregnancies and deliveries of apparently normal infants to patients treated by radiation therapy for invasive carcinoma of the uterine cervix.^{3,5,9-11} These exceptional cases are reviewed briefly and the conceivable causes are analyzed which have made the pregnancies and deliveries possible in spite of heavy irradiation of the lower uterine segment. Two additional cases are here reported, one of which resulted in the delivery of a normal-appearing infant.

REPORT OF CASES

CASE 1. This 30 year old woman had a history of 5 previous pregnancies (2 full term deliveries and 3 spontaneous abortions) when seen in the prenatal clinic of Jackson Memorial Hospital on September 11, 1958. Her last menstrual period had occurred in mid-January of 1958. Pelvic examination revealed a uterine fundus, 32 cm. in height, and an ulcerated area on the posterior cervical lip, measuring 2 cm. in diameter. The estimated time of confinement was October, 1958. A Papanicolaou smear was reported to be highly suggestive of malignant tumor, and biopsy of the cervix confirmed the diagnosis of an invasive squamous cell carcinoma of the cervix complicated by pregnancy. The remainder of the clinical and laboratory evaluation was unremarkable with the exception of a moderate degree of right hydroureter demonstrated on the excretory urogram and not attributed to the neoplasm, which was classified as Stage 1.

The patient experienced spontaneous rupture of membranes on September 18, 1958, and underwent classic cesarean section, retroperitoneal pelvic lymphadenectomy, and intracavitary radiocobalt application.

A normal-appearing female infant, weighing 4½ pounds, was delivered; no metastatic cancer was found on examination of 26 lymph nodes.

* From the Department of Radiology, Division of Radiation Therapy, University of Miami School of Medicine, Miami, Florida.

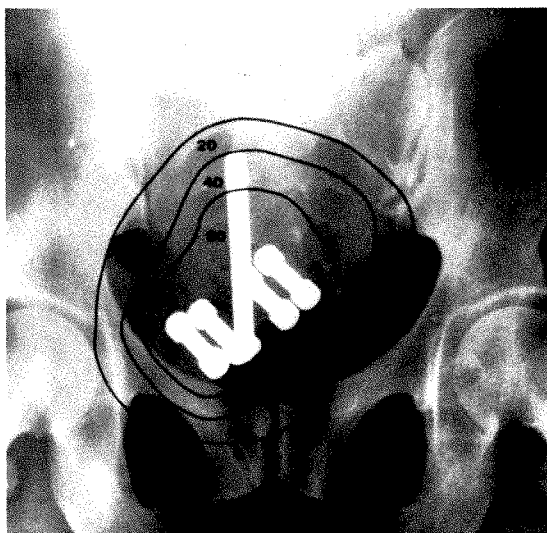


FIG. 1. Case 1. Frontal roentgenogram showing the first application of radioactive cobalt 60 isotope capsules, which remained in place for 72 hours. The numbers in the curves express the estimated gamma roentgens per hour of application.

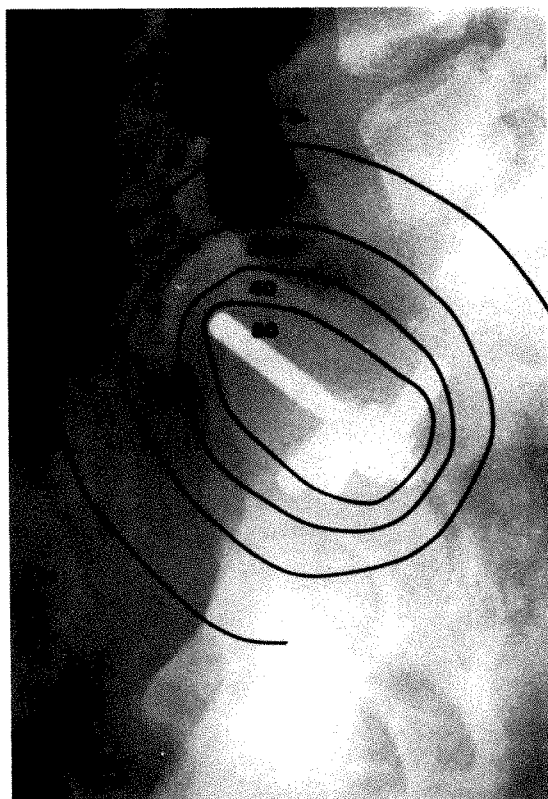


FIG. 2. Case 1. Lateral roentgenogram showing the application. This patient subsequently delivered a normal-appearing infant.

Radioisotope application consisted of a 3-source intrauterine tandem and a 4-source crossarm vaginal applicator, containing seven 6.5 millicurie cobalt 60 capsules. These applicators were left in place for a period of 72 hours. Figure 1 is an anteroposterior and Figure 2 a lateral roentgenogram of the applicators.

A second intracavitary application was performed on October 23, 1958 following a protracted and stormy postoperative course, complicated by an infected lymphocele in the vicinity of the right obturator fossa and a urinary tract infection. The application at this time comprised a 2-source intrauterine tandem and a 4-source crossarm, containing 6 capsules of cobalt 60 of 6.4 mc strength, for 24 hours, a total exposure of 4,200 mc hours (Fig. 3). After discharge, the patient was periodically examined, and the Papanicolaou smears and clinical examinations remained normal until June 28, 1960, when she was readmitted to the hospital with a diagnosis of pregnancy of an estimated 28 weeks' duration. No lesion of the cervix was at this time identified. A classic cesarean section was performed, with the delivery of a normal-appearing male infant. During surgery, numerous intra-abdominal and pelvic adhesions were noted. Some 4 months later, the patient's menstrual periods reap-

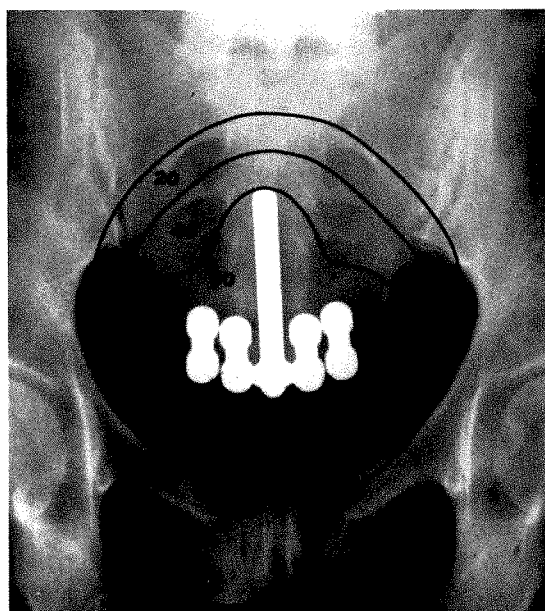


FIG. 3. Case 1. Frontal roentgenogram showing the second application of radium which was left in place for 24 hours. (For explanation, see text.)

peared and remained regular until the date of her last examination in January, 1965. At this time she was found to be in an excellent state of health. A thorough investigation has failed to reveal morphologic, developmental, or behavioral abnormalities in the boy, who was then $4\frac{1}{2}$ years of age.

CASE II. This 31 year old female was examined in the prenatal clinic on October 10, 1957. The patient had had 5 previous pregnancies. Her last menstrual period occurred in the first week of February, 1957; the estimated time of confinement was November, 1957. Examination revealed a circumferential ulceration, measuring $2\frac{1}{2}$ cm. in radius, surrounding the external os of the cervix with slightly exophytic components. There was a positive Papanicolaou smear for malignant tumor. A four-quadrant punch biopsy demonstrated invasive squamous cell carcinoma, classified clinically as Stage I. A classic cesarean section and pelvic lymphadenectomy were performed on November 7, 1957. The lymphadenectomy specimen was considered to be negative for malignant lymph node involvement. A normal-appearing male infant was delivered. Twelve days post partum, intrauterine and vaginal ap-

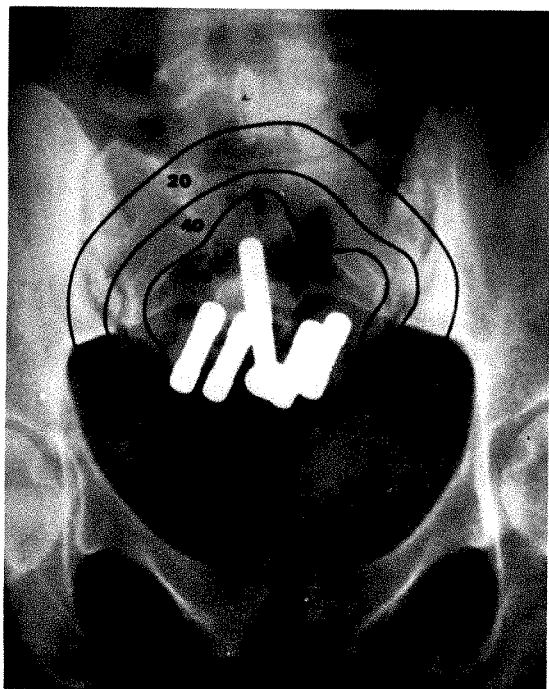


FIG. 4. Case II. Frontal roentgenogram of the pelvis showing the intrauterine and vaginal applicators, which were left in place for 72 hours.

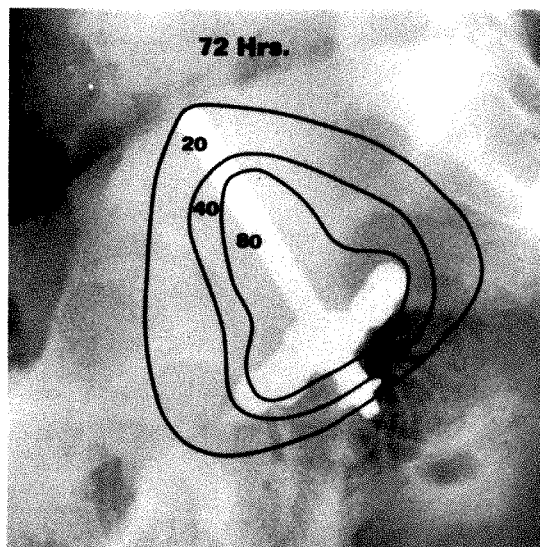


FIG. 5. Case II. Lateral roentgenogram showing the intracavitary application following cesarean section. The patient became pregnant some 56 months later.

plicators were inserted, consisting of a 2-source tandem and a 4-source crossarm, containing 6 cobalt 60 capsules of 7.2 mc strength. The system was left in place for 72 hours. The total exposure was 3,112 mc hours (Fig. 4 and 5). On follow-up examination no abnormalities were observed, and periodic Papanicolaou smears have been repeatedly negative. In May, 1958, bilateral meatotomies were done for ureterocele. At that time the Papanicolaou smear was suspicious, and fractional curettages and cone biopsy were done. The pathology report was: radiation changes with no evidence of neoplasm in the specimen. On January 14, 1959, this patient was readmitted for a repeat right ureteral meatotomy due to recurrent ureterovesical obstruction. The obstruction persisted despite surgery, resulting in chronic pyelonephritis requiring a right nephrectomy, which was done on July 30, 1959. At this time, the Papanicolaou smear was also negative. Approximately a month later, an enlarged abdominal mass was palpated. History, on admission, revealed no spotting, bleeding, or menstruation since her radium application. Pelvic examination showed an enlarged and mobile uterine fundus. A fibrotic induration without fixation of the left parametrium extending to the pelvic wall was discovered. The patient was taken to surgery 2 days later with a diagnosis of hematometria. A 11 cm. fetus was

found in the uterus. Several sections of the cervix failed to disclose persistent or recurrent tumor. On subsequent follow-up, no abnormality was noted. A normal pelvic examination was reported in November, 1963, after which the patient was lost to follow-up.

DISCUSSION

Kottmeier in 1947 thoroughly reported and discussed the various factors which might affect the dose absorbed by the ovaries upon the employment of intracavitary radium or external irradiation. It was concluded that external irradiation more often than the radium introduces irreversible changes in the ovarian follicular apparatus. Lacassagne *et al.*⁷ considered the difficulties encountered in estimating the dose-effect resulting from the irradiation of the ovary in humans. These authors expressed the opinion that the amount needed for temporary cessation of menstrual cycles would be in the area of 200 r. They also stated that 800 to 1,000 r to both ovaries would be necessary for complete sterilization. The final observations were summarized as follows:

1. There is a variable range of sensitivity of human ovaries at the different stages of development.

2. Irradiation, at times, would induce the destruction of the most radiosensitive follicles (mature and growing), while less well-developed follicles may become active again after variable intervals.

3. Permanent radiosterilization would occur only when there is a complete destruction of the entire follicular apparatus. The dose necessary to achieve similar results varies according to the age of the individual; the closer the individual is to the menopause, the lower the necessary amount of radiations.

Both Kottmeier and Lacassagne *et al.* have indicated that the position of the ovaries may vary within the pelvis. Hibbard⁴ studied the position of the ovaries of women undergoing cesarean section in the late stages of pregnancy. He plotted these organs in anteroposterior and lateral pro-

jections while the patients were under anesthesia in a supine position. It was then recognized that the ovaries, under these conditions, may be located within the radius of 10 cm. in anteroposterior projection in reference to the anterosuperior iliac spine; and they may be displaced in a frontal projection along the vertical line of 10 cm. length and 7 cm. width. This study adequately shows that there is considerable displacement of the ovaries of pregnant women, which are no longer located in the pelvis. It is thus probable that, in spite of the rather large dose of radiation delivered to the lower uterine segment in the 2 reported cases, one or both of the ovaries of our patients must have received a dose insufficient to induce irreversible changes and sterility. This point has been illustrated by plotting the distribution of energy deposited throughout the pelvis in anteroposterior and lateral roentgenograms (Fig. 4 and 5).

Allowing for an acceptable range of error, one can quite conservatively assume that, owing to the fairly high position of the sources, a minimal dose of 2,000 gamma roentgens was administered to the lateral pelvic walls and throughout the major pelvis in a matter of a few days. This amount of radiation should be considered sufficient to irreversibly damage the entire follicular apparatus.⁷

A thorough review of the literature of cases of patients reaching full term pregnancy following radiation therapy for invasive carcinoma of the cervix disclosed the following points:

1. There is a striking paucity of reports of successful pregnancies and deliveries of children to mothers treated for invasive carcinoma of the cervix. Case 1 is the third such case in the American literature and the twelfth case in the world medical literature.^{10,11} Whelton and McSweeney¹¹ summarized 9 cases and furnished a list describing details of both maternal and infant conditions. Twelve of the babies born to these patients were apparently normal in all respects. A long-term follow-up of the

babies is thus far lacking. However, 7 of these children (our case included) have been followed for a minimum of 2 to a maximum of 7 years. During this interval, these children did not show any obvious growth or developmental abnormalities.

2. In all reported cases, including our 2 patients, the tumor invariably remained confined to the cervix and, according to the International Classification, would be considered as Stage I.

3. The radiation therapy course consisted of intracavitary radium in 11 patients, and intracavitary and external irradiation in a single patient.¹⁰

4. As expected, most of the patients were young, the oldest recorded age being 35 years⁸ while the youngest was 21 years of age.¹¹

5. The actual amount of the dose delivered to the ovaries is usually impossible to evaluate. In some of the older reports there are insufficient data available and in the remaining cases, at best, the dose can be only approximately estimated. Nonetheless, the treatment resulted in control of the invasive cancer and ranged as low as 2,100 mg. hours to about 10,000 mg. hours radium equivalent material.⁴ A single case, previously mentioned, received an estimated dose of 5,600 mg. hours in addition to an estimated ovarian dose of 2,200 r via external irradiation.

6. Intracavitary radium application frequently results in adhesions and sealing of the cervicouterine canal. Therefore, it is of interest that in 3 noted instances, conization and curettage after radiation therapy might have facilitated the subsequent impregnation by establishing the patency of the canal. That ovarian function has been affected by irradiation, to a degree, is indicated by the variable periods of amenorrhea, lasting from several months to several years.

7. When one considers the variation in the position of the ovaries in late stages of pregnancy, it comes as no surprise that in 8 of these patients the applications were made during pregnancy, while in 2 instances

they were made in the immediate postpartum period. In 2 cases reported by Francis³ and Ivey,⁶ radiation therapy was administered in the absence of pregnancy. It was disclosed, however, that lymphadenectomy followed the radium application of the ulcerative type of tumor in the first of the 2 cases, while the cervix was long and the lesion exophytic in nature in the second case.

SUMMARY

Two patients in late stages of pregnancy, who were affected by invasive carcinoma of the cervix and were treated in the immediate postpartum period by intracavitary cobalt 60 sources to a dose which resulted in permanent control of the tumors and who subsequently became pregnant are reported.

One of the patients delivered an infant who has remained apparently normal up to the age of 4½ years when he was last seen.

A brief review of 11 similar cases from the literature is presented. It is concluded that the position of the ovaries immediately postpartum often results in a relatively low dose of radiation to the ovaries, and the ovarian function is resumed after variable intervals of dysfunction. All but 1 of these cases were treated by some form of intracavitary application.

A follow-up study in 7 of 13 infants born to these mothers, ranging from 2 to 7 years, showed no gross abnormalities in health and development.

Division of Radiation Therapy
University of Miami
School of Medicine
Jackson Memorial Hospital
Miami, Florida

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THE INDICATIONS FOR SELECTIVE SUPPLEMENTARY ANGIOGRAPHIC EXAMINATION IN LYMPHOGRAPHY*

By DR. T. DE ROO and A. E. VAN VOORTHUISEN
LEIDEN, NETHERLANDS

VARIOUS methods of examination have been used to establish and to determine the extent of malignant retroperitoneal processes. Fariñas² in 1947, Kaufman *et al.*³ in 1956, Holtz and Powers⁴ in 1962, Baum *et al.*¹ in 1963, Lee *et al.*⁶ in 1964, and Lindbom⁷ in 1964, as well as others used cavography and phlebography to enable them to evaluate retroperitoneal metastases. With the use of arteriography, Fernström³ obtained information on the nature and extent of malignant processes in the uterus and adnexa. These angiographic investigations are especially performed for the purpose of determining the existence of possible metastases in lymph node packets. The lymph nodes are situated around the arteries and veins and, if enlarged, characteristic impressions on the blood vessels may be demonstrated.

With the advent of lymphography for visualization of the lymphatics, the above mentioned procedures became less popular. Using lymphography, it is possible to demonstrate malignant processes causing pathologic changes in lymph nodes and to determine their extent. The localization of pathologic lymph nodes in the pelvis and/or abdomen can be accurately done by lymphography, thus making directed therapy possible. This is important since retroperitoneal spread of a malignant process is often suspected but usually cannot be evaluated clinically. Unfortunately, lymphography does not always furnish adequate information; fairly often some groups of lymph nodes are not visualized. This may be due to the following reasons: (1) pathologic changes in the lymph nodes causing them to lose their contrast-absorbing prop-

erties; and (2) absence (congenital) of lymph nodes without any pathology being present.

The 2 cases to be described are examples of such instances.

ILLUSTRATIVE CASES OF LYMPHOGRAPHY

CASE I. Mr. J.M. (16726/63). This 35 year old male had a history of Hodgkin's disease for a number of years. He had received radiotherapy to the neck, axilla, and hilar region. In November, 1963 he was admitted to the hospital. On physical examination irregular masses were found in both groins and lymphography was performed.

Lymphograms demonstrated numerous, greatly enlarged lymph nodes, along with congested collateral lymphatics in the pelvis and lower abdomen. A lymphadenogram (Fig. 1) showed the lymph nodes to be nodular and partly mottled, characteristic of Hodgkin's disease. Above the level of the fourth lumbar vertebra, no lymph nodes were visualized. Because of the poor general condition and the extent of the process, the patient was treated with vincoleukoblastine. He died on February 1, 1964. On obduction, a large, matted conglomeration of lymph nodes was found at the level of the first four lumbar vertebrae.

CASE II. Mrs. B.D-C. (2170/64). This 61 year old woman was admitted to the hospital in September, 1964 for flux in the menopause. On curettage, an adenocarcinoma of the corpus uteri was found. In view of this finding, lymphography was performed. On the lymphogram, the contrast material filled the lymphatic system up to the fifth lumbar vertebra, but not beyond that point. In the pelvis, extremely congested collateral lymphatics were visible. The lymphadenogram (Fig. 2) demonstrated enlarged lymph nodes which appeared to be inflamed and hypertrophic. Roentgenograms

* From the Department of Radiology, University Hospital, Leiden, The Netherlands. Head: Prof. Dr. J. R. von Rennen.



FIG. 1. Case 1. Hodgkin's disease. Lymphadenogram showing impairment of drainage of the lymphatic stream at the level of the fourth lumbar vertebra. On obduction, a large matted lymph node packet was found extending from the first to the fourth lumbar vertebra.

taken after 72 hours demonstrated no visualization of the lymph nodes above the level of the 5th lumbar vertebra.

On September 19, 1964 the patient was operated upon. The uterus and adnexa were removed. In the paralumbar and aortic region, no lymph nodes were found. Histologically, the lymph nodes extirpated from the iliac region showed changes suggestive of inflammation but no metastases.

Comment. The lymphograms of both Case 1 and Case 11 showed nonfilling above the level of the fourth to fifth lumbar vertebra. In Case 1 on obduction, pathologic lymph nodes were found at this site; in Case 11 surgery revealed the congenital absence of lymph nodes at this site.

On studying these lymphographic findings, it becomes clear that a supplementary investigation of the blood vessels is necessary. Since the site of the doubtful area is

visualized on the lymphogram, the supplementary angiography (cavography, phlebography and/or Seldinger arteriography) can be a selective one.

ILLUSTRATIVE CASES OF LYMPHOGRAPHY SUPPLEMENTED BY ANGIOGRAPHY

The case records of some patients in whom lymphography was followed by selective angiography which supplied important diagnostic data are presented below.

CASE 111. Mrs. M.J.C.H.-B. (6091/65). This 54 year old woman received radiotherapy for carcinoma of the cervix uteri in 1957. In August, 1964 she was admitted to the hospital. She was then complaining of pain in the right groin; the erythrocyte sedimentation rate was increased, and on physical examination a tumor or inflammatory infiltration was palpated at the right pelvic wall.

Roentgenologic examination of the pelvis

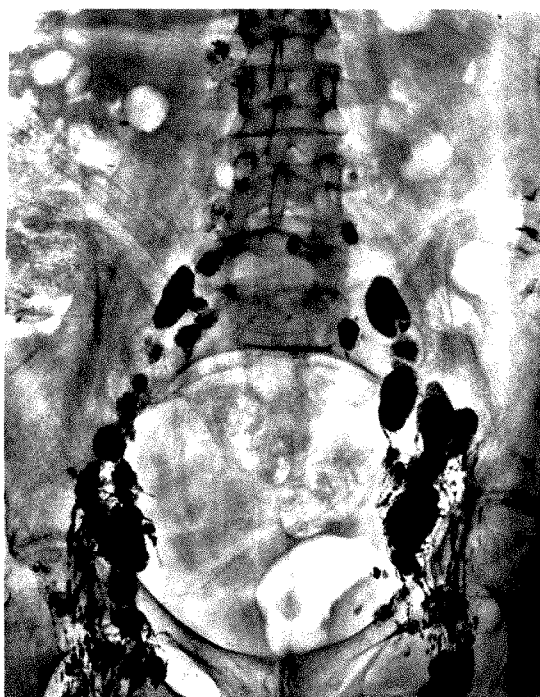


FIG. 2. Case 11. Carcinoma of the corpus uteri. Lymphadenogram showing impairment of drainage of the lymphatic stream at the level of the fifth lumbar vertebra. At operation, no lymph nodes were found in the vicinity of the first to fifth lumbar vertebrae.

and colon revealed no abnormalities. On the lymphogram, a blockage of the contrast material was seen low in the right iliac region (Fig. 3). In the left lymphatic system, no abnormalities were detected. To obtain more information on the area above the blockage, a phlebocavogram was made (Fig. 4). The right external iliac vein appeared to be narrowed just above the last filled lymph nodes on the lymphadenogram and to curve medially. The common iliac and the caval vein showed no abnormalities. A diagnosis of metastases to the lymph nodes was made. Radiotherapy effected marked regression of the process.

CASE IV. Mrs. M.-K. (19566/64). This 43 year old woman underwent palliative supravaginal total hysterectomy and bilateral complete oophorectomy for bilateral carcinoma of the ovaries with metastases in the Douglas pouch in April, 1964. Postoperatively, she had been treated with chemotherapeutic agents. In December, 1964 she was re-admitted to the hospital because an increase in the tumorous tissue, that had been left behind at opera-

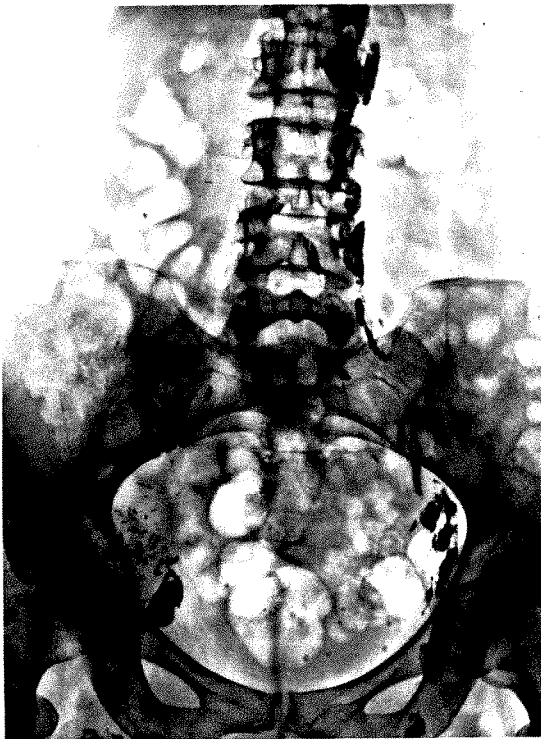


FIG. 3. Case III. Carcinoma of the cervix uteri. Lymphadenogram showing a complete block in the right iliac region.



FIG. 4. Case III. Carcinoma of the cervix uteri. Phlebocavogram showing a narrowed right iliac vein curving medially just above the last filled lymph node on the lymphadenogram (Fig. 3).

tion, was detected on gynecologic examination. Lymphography was performed to determine whether pathologic lymph nodes were present in the abdomen. On the lymphograms, a blockage was seen on the right side at the level of the 4th lumbar vertebra; below this, the lymphatics were congested. On the lymphadenogram, none of the lymph nodes on the right side above the blockage had filled with contrast material (Fig. 5a). No other abnormalities were detected in the lymphatic system. For further analysis of the nonvisualized area, a cavogram was made. The anteroposterior and lateral roentgenograms showed smooth and perfect contours and a normal intensity of contrast material was demonstrated in the inferior caval vein (Fig. 5, b and c). The normal cavogram made the presence of lymph node metastases above the site of the impairment of drainage, noted on the lymphogram, unlikely. The limited spread of metastases ap-

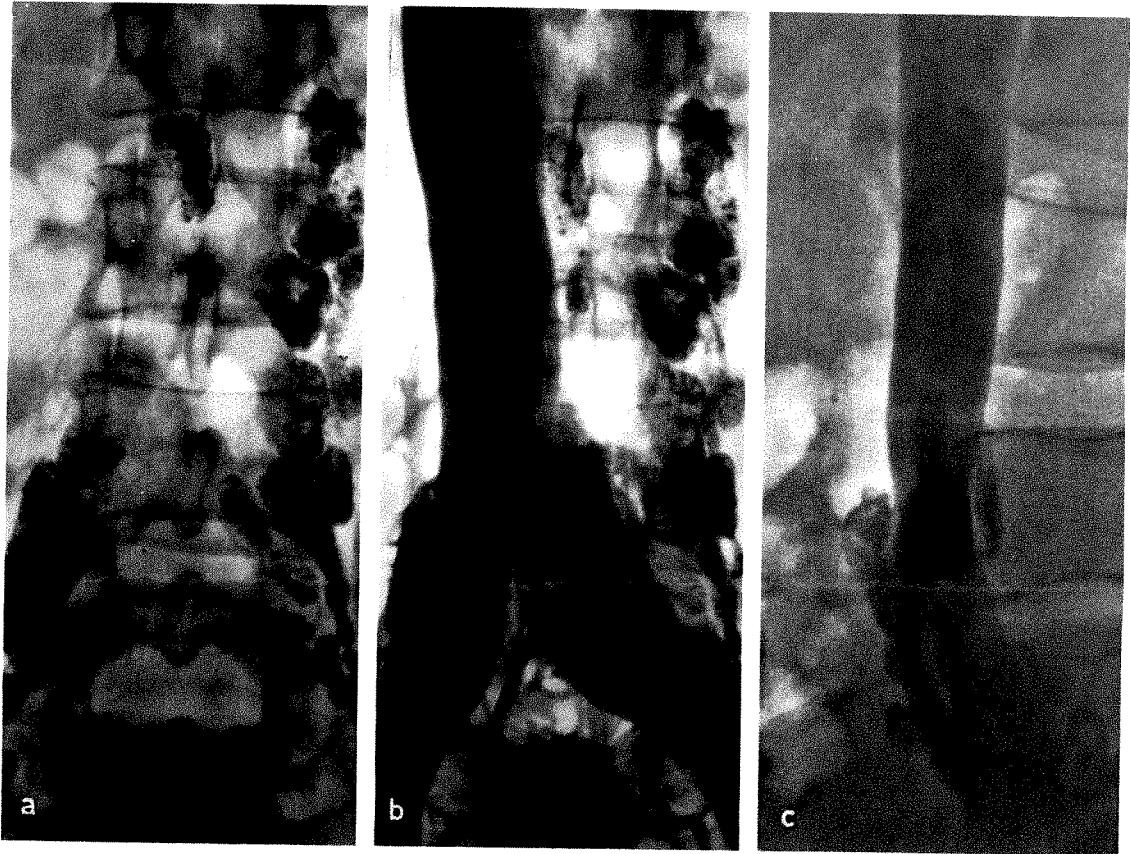


FIG. 5. Case IV. Carcinoma of the ovaries. (a) Lymphadenogram showing normal para-aortic and paralumbar lymph nodes on the left. On the right, no lymph nodes are visualized above the fourth lumbar vertebra. (b and c) Anteroposterior and lateral cavograms showing normal filling of the inferior caval vein above the site of impairment of drainage on the lymphadenogram (a).

peared to be an indication for curative roentgen therapy to the pelvis minor (tumor dose, 6,000 r). This treatment resulted in almost complete disappearance of the tumor infiltration.

Comment. In both Case III and Case IV, a blockage of contrast medium was found in the lymphadenogram, and, therefore, selective angiography was performed. In the first patient, a compression of the vessels demonstrated the presence of pathologic lymph nodes in the nonvisualized region. In the second patient, the vascular course was absolutely normal, which made the existence of pathologic lymph nodes very unlikely.

CASE V. Mrs. B.W.-B. (19443/64). This 60 year old woman received radiotherapy in March, 1958 for a carcinoma solidum (Stage 3)

of the cervix uteri. She had reacted well to this treatment and for years had been without symptoms. In November, 1964 she complained of fatigue and pain in the back. She also showed an increased erythrocyte sedimentation rate. Lymphography was performed for possible metastases in the lymphatic system. On the lymphadenogram, an interruption of the lymphatic chain was visualized in the right paralumbar region from the second to the fourth lumbar vertebra (Fig. 6a). On laminagrams (Fig. 6b), the visualized paralumbar and aortic lymph nodes appeared normal. Therefore, cavography was performed. On the lateral roentgenogram (Fig. 6c), the inferior cava showed an impression, indicating the presence of lymph node metastasis. This patient received palliative roentgen therapy.

CASE VI. Mr. J.M.K. (20283/64). This 35 year old man was admitted to the hospital in

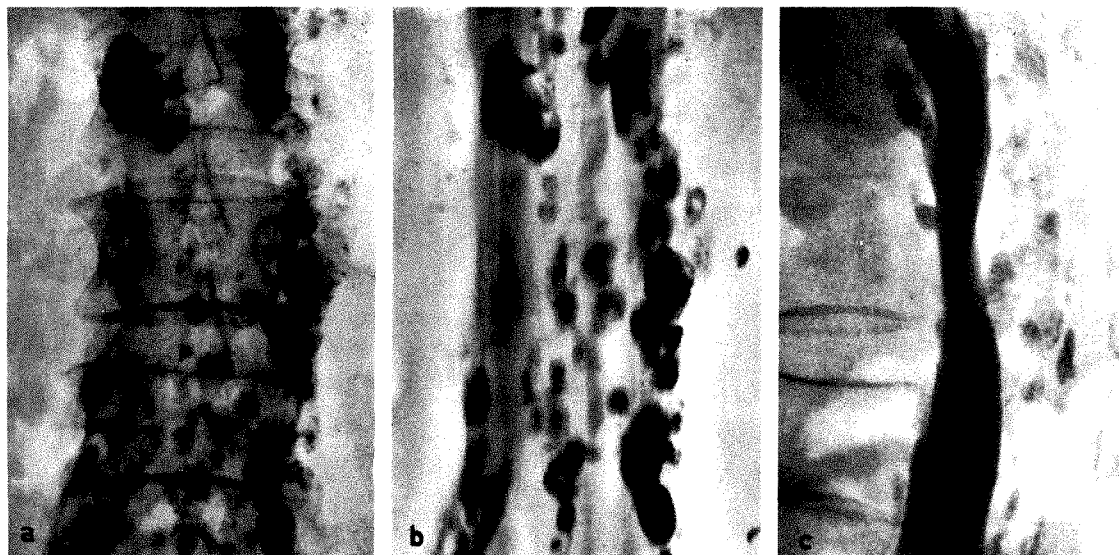


FIG. 6. Case v. Carcinoma of the cervix uteri. (a) Lymphadenogram showing interruption of the right paralumbar lymph node chain at the level of the third lumbar vertebra. (b) Laminagram showing roentgenologically normal lymph nodes. (c) Lateral cavogram revealing an impression on the inferior caval vein on the ventral side at the level of the interruption in the lymphatic chain.

December, 1964 for recurrent hematuria. On cystoscopy, a large ulcer was detected on the anterior side of the bladder. The pathologic

diagnosis was carcinoma of the urinary bladder infiltrating into the muscle layer. Lymphography was performed for demonstration of pos-

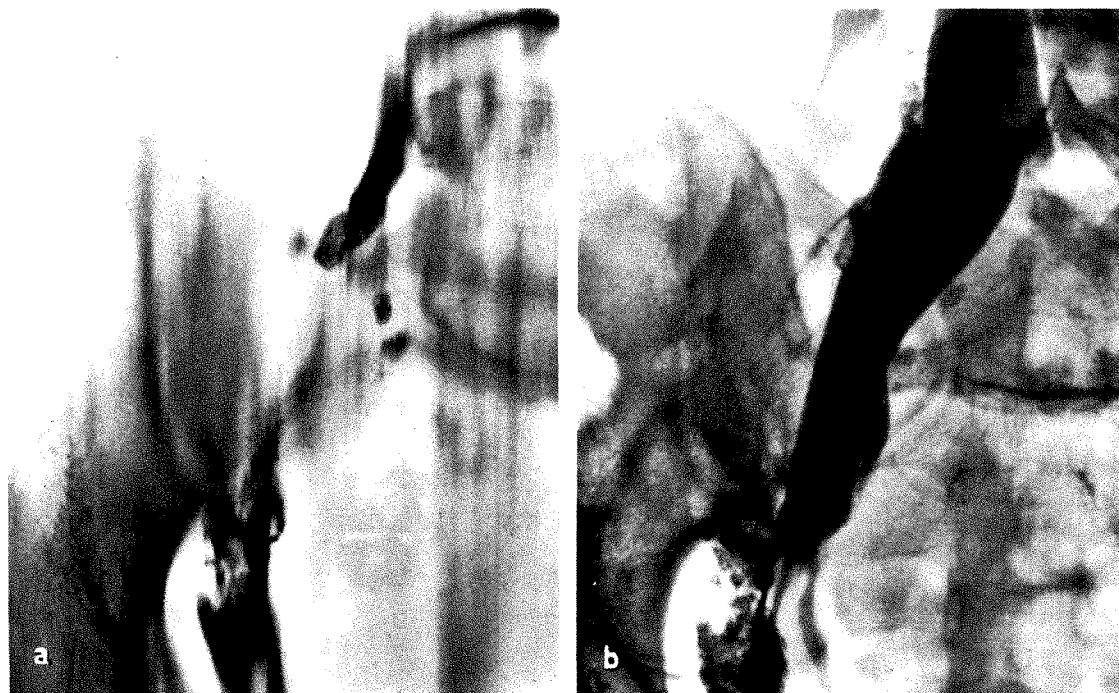


FIG. 7. Case VI. Carcinoma of the urinary bladder. (a) Laminagram showing interruption of the lymphatic chain at the level of the common iliac vein. (b) Phlebogram showing normal filling of the right common iliac vein.

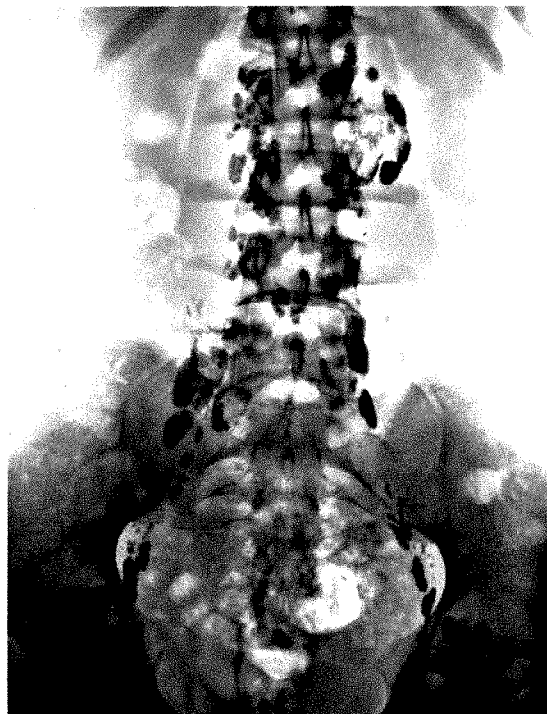


FIG. 8. Case VII. Tumor of the testis. Lymphadenogram showing a pathologic area in the left paralumbar region. In the right low paralumbar region there is a doubtful area, composed of a number of enlarged and partly superimposed lymph nodes and some undefinable spots of contrast material. The internal structure and marginal sinus of these lymph nodes cannot be evaluated accurately.



lymphadenogram, the common iliac vein showed smooth, perfect contours and there was normal contrast intensity (Fig. 7*b*). The normal phlebogram made the presence of lymph node metastases unlikely.

At operation, no lymph nodes were found in the region of the right common iliac vein.

Comment. In contrast to Cases III and IV Cases V and VI showed a nonvisualized area around which normally filled lymph nodes were present. By supplementary angiographic investigation, it was demonstrated that in Case V the nonvisualized area was due to pathologic lymph nodes, whereas in Case VI no lymph nodes were present.

CASE VII. A.G.H. (12/65). This 18 year old youth underwent a right orchiectomy for a testis tumor (composed of embryonic carcinoma, teratoma and seminoma) in January

sible metastases. On the lymphadenograms (with supplementary laminagrams), there appeared to be an interruption over a 7 cm. area in the lymphatic chain on the right side (when compared to the left) in the region of the common iliac vein (Fig. 7*a*). Supplementary phlebocavography was indicated. At the site of the interruption in the lymph node chain on the



FIG. 9. Case VII. (*a* and *b*) Tumor of the testis. Laminagrams of the left paralumbar pathologic region showing 3 matted, enlarged and metastatic lymph nodes displacing some normal paralumbar lymph nodes laterally.

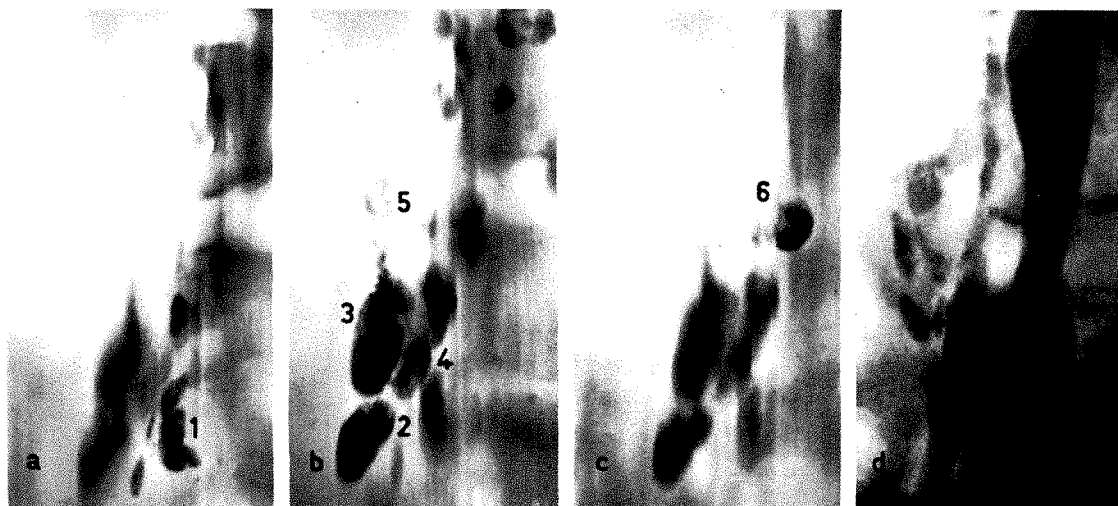


FIG. 10. Case VII. Tumor of the testis. (*a*, *b* and *c*) Laminagrams and (*d*) cavogram of the doubtful right paralumbar region. Although lymph nodes 1, 2, 3 and 4 are normal as far as the marginal sinus and internal structure are concerned, they are enlarged as though affected by inflammation. On *b* no explanation for the spots of contrast material (5) was found but on *c* another normal lymph node (6) was visualized. On the lateral cavogram (*d*), a marked impression is visible on the ventral side.

1965. Clinically, there were no signs of metastases. Lymphography was performed for possible metastases to the lymphatic system. On the lymphadenogram, the left paralumbar region showed a pathologic area (Fig. 8). Laminagrams showed 3 matted, enlarged metastatic lymph nodes, displacing some normal paralumbar lymph nodes laterally (Fig. 9, *a* and *b*). In the right lower paralumbar region, a number of enlarged and partly superimposed lymph nodes and some indefinable spots of contrast medium were visible. The internal structure and the marginal sinus of these lymph nodes could not be evaluated accurately. Additional laminagrams (Fig. 10, *a*, *b* and *c*) showed that lymph nodes 1, 2, 3, and 4 had the aspect of lymph nodes affected by inflammation combined with hypertrophic changes. Specks of contrast material could not be evaluated on one laminagram (5 in Fig. 10*b*), a normal lymph node was seen on another study (6 in Fig. 10*c*). An anteroposterior cavogram showed a slight decrease of contrast in the inferior caval vein in the doubtful region. A lateral roentgenogram (Fig. 10*d*), made at the same level, showed a marked impression on the ventral side, indicating the presence of pathologic lymph nodes.

In view of the findings on lymphadenograms and cavograms, the patient was operated upon. The roentgen diagnosis was confirmed at operation as well as on pathologic examination.

CASE VIII. Mr. R.K. (2763/65). This 20 year old man received radiation therapy in September, 1964 for a reticulosarcoma in the neck and both axillae. In February, he was re-admitted to the hospital because of enlarging lymph nodes in the neck. He also complained of pain in the back. A lymphographic examination was performed for the detection of possible retroperitoneal pathologic lymph nodes. On lymphograms (Fig. 11*a*) as well as on lymphadenograms (Fig. 11*b*), a doubtful area was seen in the right paralumbar region. Laminagraphy did not clearly indicate whether just one enlarged and grossly affected lymph node, or a number of small normal lymph nodes arranged in a circle and simulating metastatic affection was present (Fig. 12*a*).

On supplementary angiograms, the anteroposterior and lateral views (Fig. 12*b*) of the inferior caval vein showed smooth perfect contours and normal contrast intensity. The presence of a large pathologic lymph node in the doubtful region was judged to be very unlikely and no radiotherapy was given to the abdomen. The patient has been kept under control for some time; no clear abdominal localization of reticulosarcoma has manifested itself.

Comment. From Cases VII and VIII, it becomes clear that the evaluation of localized manifestations of grossly affected

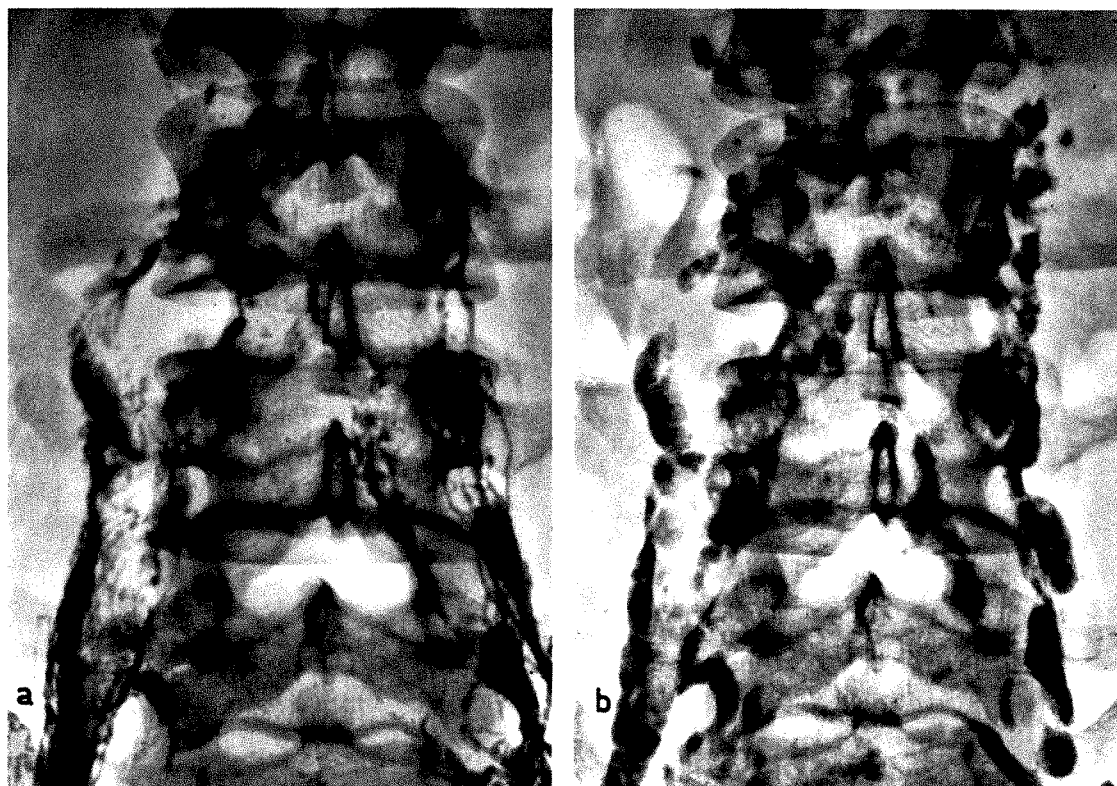


FIG. 11. Case VIII. Reticulosarcoma. (a) Lymphogram and (b) lymphadenogram showing a doubtful area in the right paralumbar region.

lymph nodes poses many difficulties even after laminagraphy. Supplementary angiographic studies proved to be very valuable in these cases. In Case VII they demonstrated the pathologic lymph nodes; in Case VIII they excluded to a high degree the probability of the presence of pathologic lymph nodes.

DISCUSSION

A complete or almost complete blockage of contrast material is sometimes demonstrated on a lymphogram which may or may not be combined with distinct impairment of drainage. Such a nonvisualized area may also be the result of partial interruption of the lymphatic chain. Finally, some lymph nodes may be so poorly filled with contrast medium that even with supplementary laminagraphy, the normality or abnormality of these lymph nodes cannot be determined.

In such cases, as has been illustrated by the case histories, selective angiography may be very useful. Phlebography and cavography are techniques which appear to be best suited for the demonstration of pathologic lymph node packets. These studies complement the lymphographic findings. The method consists of one or two catheters being placed in such a way that maximum filling of the vessel in the suspected area is obtained. Exposures are made in two directions: pelvic vessels in the anteroposterior and oblique positions and the inferior caval vein in the anteroposterior and lateral positions. Also pathologic lymph nodes may be demonstrated by means of arteriography or aortography, especially in the pelvis minor. A distinctly recognizable impression on an artery is, however, to be expected at a later stage than the compression of a vein. An advantage of arteriography is that compression



FIG. 12. Case VIII. Reticulosarcoma. (a) On the laminagram, it is not possible to establish with any certainty whether the doubtful region in Figure 11, *a* and *b* is composed of one large, extremely pathologic lymph node or of a number of small, normal lymph nodes, confusingly arranged in a circle. (b) Lateral cavogram showing a smooth, perfect contour of the inferior caval vein and a normal intensity of contrast.

of an artery cannot be confused with physiologic narrowing, as may occur in the venous system in which physiologic compression is caused by organs, arteries, tendons and bony ridges.

SUMMARY

In 15 per cent of our lymphographic examinations, filling with contrast medium of the lymph nodes was insufficient for complete evaluation.

The main limitations were: (1) nonvisualization above a complete blockage or impairment of drainage; (2) nonvisualization presenting as an interruption of a lymph node chain; and (3) poorly filled

lymph nodes, which could not be evaluated accurately even on laminagrams.

Selective angiography (phlebography, cavography) often provided important data on the doubtful areas in such instances.

In a department where lymphography is practiced, supplementary angiography is indispensable.

Dr. T. de Roo
Central Ziekenhuis
Alkmaar, Netherlands

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THE RADICAL TREATMENT OF ENLARGED LYMPH NODES IN MALIGNANT MELANOMA

By T. F. SANDEMAN, M.D., F.F.R.
MELBOURNE, AUSTRALIA

THE patient with an early malignant melanoma or in the disseminated stage of the disease presents few problems of a philosophical nature. In one, radical therapy is essential and in the other, palliation is all that can be offered. Between lies the group in which there are clinically significant lymph nodes without proven dissemination. Although cure appears possible, the published results are disappointing. Petersen *et al.*³³ called therapeutic dissection only marginally useful, but did not state what should be used in its place.

In many reports, the results in this category of patients are obscured by the method of presentation. If only cases operated on are included and the survivorship is calculated according to whether tumor was found in the lymph nodes or not, this will shed no light on what to advise an individual patient who presents with regionally advanced disease at an apparently curable stage. Elective and therapeutic dissections are too often combined to give a distorted picture of the results in each. Treatment, other than radical surgery is seldom used except as a palliative measure. Since other methods have been in use in Melbourne and adequate records kept, it was thought to be of interest to review the results.

MATERIAL

A review of all cases of malignant melanoma referred to the Radium Department of the Royal Melbourne Hospital and the Peter MacCallum Clinic was undertaken. The total case material was staged on clinical grounds alone, *viz.*, Stage I: disease confined to the primary site; Stage II: palpable but operable regional lymph nodes; Stage III: inoperable regional lymph nodes; and Stage IV: distant metastases. After exclusion of all those with doubtful histologic evidence, junctional nevi, super-

ficial melanocarcinoma,¹ juvenile melanoma²⁴ and Stage IV cases, it was possible to obtain a group with invasive melanoma apparently confined to a region and within the limits of radical treatment. The Stage I patients who had adequate treatment to the primary lesion have been reported elsewhere while assessing the value of elective treatment of the lymph nodes.³⁸ Of this group there were 6 who had positive lymph nodes on elective dissection and 50 others who had no elective treatment but developed enlarged regional lymph nodes during the course of observation. To these are added 11 cases in which the primary lesion was not adequately dealt with but the draining lymph nodes enlarged after presentation. This group is designated originally Stage I (67 cases). The 40 Stage II cases include 1 woman who presented with a mobile lymph node mass but no discoverable primary lesion. In 3 others the primary lesion was never histologically confirmed as it healed spontaneously or following accidental trauma, leaving only a small scar. This probable primary site has been recorded. There were only 6 patients in whom inoperable lymph nodes were not accompanied by distant metastases. Tables I and II show the ages of the patients and the sites of the primary lesions by sex and stage.

RESULTS

Survival rates were calculated on a cumulative basis from the time of treatment of the lymph nodes and not from the time of treatment of the primary lesion, which in many Stage I cases preceded this date by many years. Two Stage I patients in whom the lymph node enlargement appeared in 1963 were, therefore, not assessable and, although included in Tables I and II, do not appear in the survival calculations.

TABLE I
AGE, SEX AND STAGE AT PRESENTATION

Age (yr.)	0-15		16-25		26-35		36-45		46-55		56-65		66-75		76-85		86-		?	Total No.	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	M	F
Stage I	1	0	2	3	5	8	9	6	4	9	5	6	4	4	0	0	0	1	0	30	37
II	0	1	3	1	2	5	5	1	8	5	2	1	3	2	1	0	0	0	1	24	16
III	0	0	1	0	0	0	2	1	0	1	0	1	0	0	0	0	0	0	0	3	3
All Cases	1	1	6	4	7	13	16	8	12	15	7	8	7	6	1	0	0	1	1	57	56

In Table III and Figure 1, the 3 and 5 year cumulative survival figures are presented according to the method of treatment used. Surgery and radiation over-all produced almost equal survival rates. Omitting the electively dissected cases with positive lymph nodes actually improved the surgical figures. The combined policy, in which excision of one lymph node, usually without formal dissection, was followed by irradiation with external or implanted sources, produced better results than either surgery or radiation therapy alone in 6 patients who were originally Stage I. There is no likely explanation except chance to explain why it was unsuccessful in 4 Stage II cases. It is noteworthy that an appreciable survival rate was obtained in 6 patients who had inoperable

lymph nodes and received irradiation alone. Although 4 of 6 cases who refused or were denied treatment survived 3 years, all had died before 5 years.

Of 95 cases available for cumulative study at 10 years, 9 survived (9.5 per cent), all but one having had irradiation at some stage to recurrent lymph nodes.

While survival rates are the best method of comparing different policies of management, a study of subsequent events and the end results can add to the information which can be extracted from any series. Table IV shows that 25 patients remain alive and well from 6 months to 24 years following treatment, although 2 of them had no tumor in the excised lymph nodes. Of the surviving patients, further treatment was required in 9. Four had additional

TABLE II
SITE, SEX AND ORIGINAL STAGE

	Head and Neck		Upper Limb		Trunk		Leg		Foot		Eye		Genital		?	Total No.	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	F	M	F
Stage I	13	10	1	1	8	6	4	16	3	3	1	0	0	1	0	30	37
II	8	2	2	1	5	5	6	7	3	0	0	0	0	0	1	24	16
III	0	0	0	1	1	0	2	0	0	2	0	0	0	0	0	3	3
All Cases	21	12	3	3	14	11	12	23	6	5	1	0	0	1*	1	57	56

Note: In 3 patients the site of the primary lesion was not established with certainty but the likely site has been used. * In 1 case, no possible primary lesion or scar could be found.

TABLE III

THE CUMULATIVE 3 AND 5 YEAR SURVIVAL RATES ACCORDING TO THE TYPE OF TREATMENT
AND THE ORIGINAL STAGE OF DISEASE AT PRESENTATION

	Stage I		Stage II		Stage III		Total Series	
	3 years	5 years	3 years	5 years	3 years	5 years	3 years	5 years
Surgery	14/36*	9/34	10/22	6/22	—	—	24/58	15/56
Per Cent	39	27	45	27	—	—	41	27
Irradiation	7/22	5/22	4/9	3/9	4/6	2/6	15/37	10/37
Per Cent	32	23	44	33	67	33	40	27
Combined Treatment	4/6	4/6	0/4	0/4	—	—	4/10	4/10
Per Cent	67	67	0	0	—	—	40	40
No Treatment	1/1	0/1	3/5	0/5	—	—	4/6	0/6
Per Cent	100	0	60	0	—	—	67	0
Total	26/65	18/63	17/40	9/40	4/6	2/6	47/111	29/109
Per Cent	40	29	42	22	67	33	42	27

* Including 6 elective dissections with only 1 survivor, *i.e.*, for therapeutic dissections alone, the true 3 year survival is 13/30 (43 per cent) and 5 year survival 9/30 (30 per cent).

surgery—one following radiotherapy—and 4 had irradiation in one form or another. The ninth was given a course of cyclophosphamide for what was thought to be cerebral metastases. The neurologic findings, however, were equivocal, no biochemical or histologic proof was obtained and the patient has remained well for the last 3 years without further treatment, which all suggest that the symptoms and signs could have had another explanation.

DISCUSSION

The extent of the problem can be gauged from the incidence of Stage II patients in recent reports, ranging from 25 per cent of the cases reported by Guiss and MacDonald,¹² 39 per cent by Price and DuVal,³⁵ 53 per cent by Southwick *et al.*⁴⁰ to 61 per cent by Fortner *et al.*¹⁰ Das Gupta and McNeer⁴ found metastases in the accessible lymph nodes of 80 per cent of patients but this included nonregional groups for the site, and ignored the possibility of concomitant hematogenous spread. In the present series, the incidence of Stage II cases at presentation was 14.2 per cent although the total, including inoperable and originally Stage I patients, represents 39 per cent of the 282 invasive melanomas avail-

able. This includes 6 electively dissected cases in which lymph nodes were found to be involved on section. Only 1 of these 6 survived 3 years.

Block and Hartwell² claim that clinical assessment of lymph node involvement is

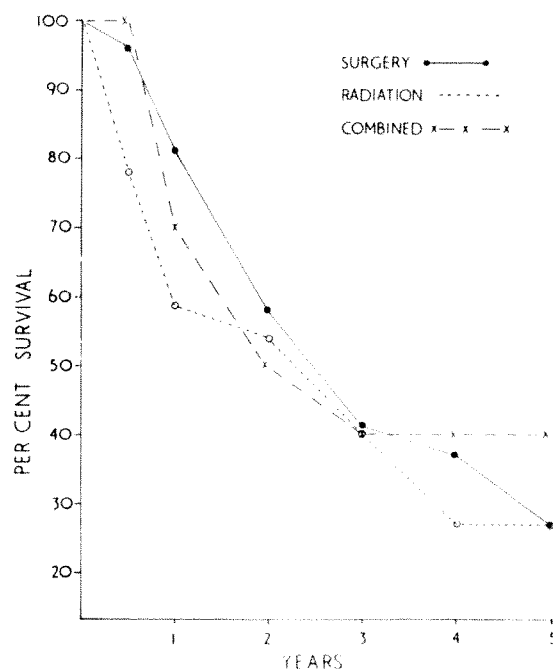


FIG. 1. Cumulative survival rates according to type of treatment.

TABLE IV
FINAL STATUS OF PATIENTS IN SERIES

Present State	Surgery	Range of Survival	Radiation Therapy	Range of Survival	Combined Treatment	Range of Survival	No Treatment	Range of Survival
Alive and Well	16	6/12 to 24 years	5	12/12 to 22 years	4	9 years to 16 years	0	
Later Treatment	8 none, including 2 with no tumor in excised lymph nodes; 3 had further surgery; 4 radiation therapy or implant; 1 chemotherapy for unconfirmed cerebral metastases		4 none; surgery		4 none			
Dead of Melanoma	37	7/12 to 12 years	29	2/12 to 10 years	6	11/12 to 5 years	4	3 years to 4 years
Dead of Other Causes	1	2½ years	1	2½ years	0		0	
Lost to Follow-Up	4	4/12 to 1 year	2	2 years to 3 years	0		2	0-12/12

90 per cent accurate. Fortner *et al.*¹⁰ found only 2 negative results in 77 cases in which lymph nodes were definitely thought to be the site of tumor (97.4 per cent accuracy) and were right in 77 per cent of those they considered to be suspicious. Of 68 cases in this report in which a pathologic examination was made of excised lymph nodes, 2 were found free of disease, which suggests a similar level of clinical accuracy.

When a critical examination is made of the literature on the results of treatment in Stage II melanoma, many reports are disappointing in that they do not separate this group from Stage I cases with positive lymph nodes on elective dissection,^{3,10,12,20} no time interval is specified^{30,35} or the entire material is not used in the calculations.⁴⁰ However, even with these deficiencies, there is a surprising uniformity in the survival rates of the therapeutically treated series. Most, even when Stage I positive cases are included, lie in the range of 20 to 30 per cent alive at 5 years. The over-all 5 year cumulative survival, which is slightly lower than the determinate available figure used in the quoted works, in

this report is 27 per cent. Guiss and MacDonald¹² in 1962 claim higher figures of 31.4 to 40 per cent, depending on the number of lymph nodes involved at histologic examination, but McWhirter^{22,23} and Sandeman³⁸ have pointed out that results can vary markedly with this method of presentation.

In all the series quoted surgery has been used as the main method of attack but there have been recent reports^{14,15} suggesting that the tumor is not so completely radioresistant as most clinicians believe. These have revived the interest occasioned by such papers as that of Owen,³¹ who recorded a 3 year survivor with radiation therapy after multiple surgical recurrence. Keith and Keith,¹⁸ Quigley,³⁶ Scharnagel,³⁹ Ellis,^{8,9} and Tod⁴³ reported series in which radiation had been extensively used with results comparable to those of surgery. Some Scandinavian,^{6,17,29,42} German,^{18,14,27} and Russian centers^{21,26} have placed considerable reliance on irradiation, at least as an adjunct. On the other hand, in many textbooks of surgery⁸ and even radiotherapy^{19,24} irradiation has been condemned as

useless or dangerous. Indeed, Paterson³² stated that any malignant melanoma which was locally cured by radiotherapy was probably not a malignant melanoma. It is unfortunate that such a dogmatic statement has received more attention than reports such as those of Dickson,⁵ showing an increase in the survival rate with the use of postoperative radiotherapy following dissection.

Jantet *et al.*¹⁶ put forward intralymphatic irradiation as a less traumatizing—and in a small series—a more effective method of dealing with lymph node spread at the elective stage than dissection, but Green³¹ has pointed out that in the presence of even minor enlargement of the lymph nodes the dosage falls off so quickly that this method cannot deliver a comparable quantity of radiation to the entire tumor volume.

If it is conceded that irradiation can control some cases of malignant melanoma, it can be argued that its use as part of a radical policy in moderately advanced cases would allow a proper assessment of its place in the treatment of the disease. The question then arises as to where and when it would be best employed. From the encouraging results in a few combined therapy cases, it would appear that surgery plus radiotherapy has a better chance than either alone. There is evidence that preoperative radiotherapy is of considerable value in many situations where the tumor is relatively radioresistant.^{23,41} It would seem not unreasonable to duplicate this scheme in malignant melanoma, thus avoiding the morbidity associated with the excessively high and possibly repeated doses of radiation occasionally employed to eradicate persistent lymph node enlargement. An example of such a policy is Case I below. Case II illustrates a prolonged survival associated with extreme morbidity from irradiation employed alone. Case III demonstrates the excellent palliation which can be obtained in some cases. Hyperbaric radiotherapy may improve the results of irradiation even more²⁵ but the long term

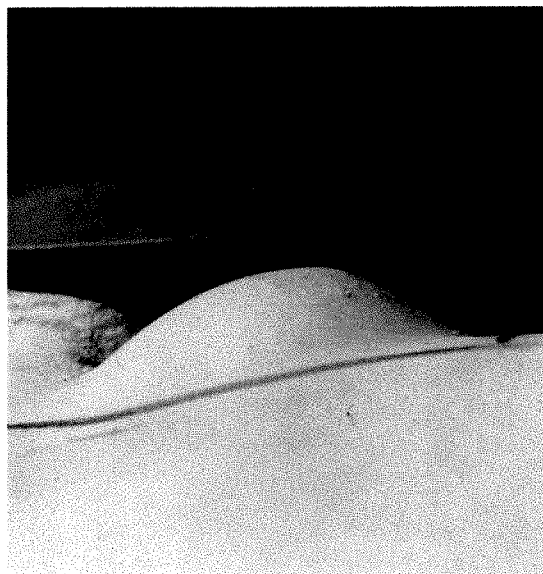


FIG. 2. Case I. The mass in the groin prior to irradiation. The outline of the lower lateral corner of the radiation field can be seen.

effects and the outcome of preoperative treatment have yet to be assessed.

REPORT OF CASES

CASE I. Female, aged 35 years. In 1952 a bleeding mole was excised from the patient's right calf and the specimen was discarded without histologic examination. Eighteen months later she noted a lump in the right groin at which time she was pregnant. It grew slowly but after the birth of her baby and during lactation it increased rapidly in size. Her local physician took a biopsy which showed malignant melanoma and referred her to the Peter MacCallum Clinic.

Clinical examination revealed a 7.5×5 cm. hard fixed mass over the right saphenous opening with an overlying biopsy scar. It was elevated 5 cm. Superiorly, there was a separate 1.0 cm. firm mobile node and nodes could be felt above the inguinal ligament in the external iliac group. The primary site remained clear. No mass was felt in the pelvis (Fig. 2). A further drill biopsy was taken to confirm the diagnosis (Fig. 3, A and B).

From August 4, 1955 to November 17, 1955, 26 treatments were given at twice or thrice weekly frequency with a half value layer of 1.0 mm. Cu to a 10×20 cm. field covering the palpable disease. The total skin dose was 6,000

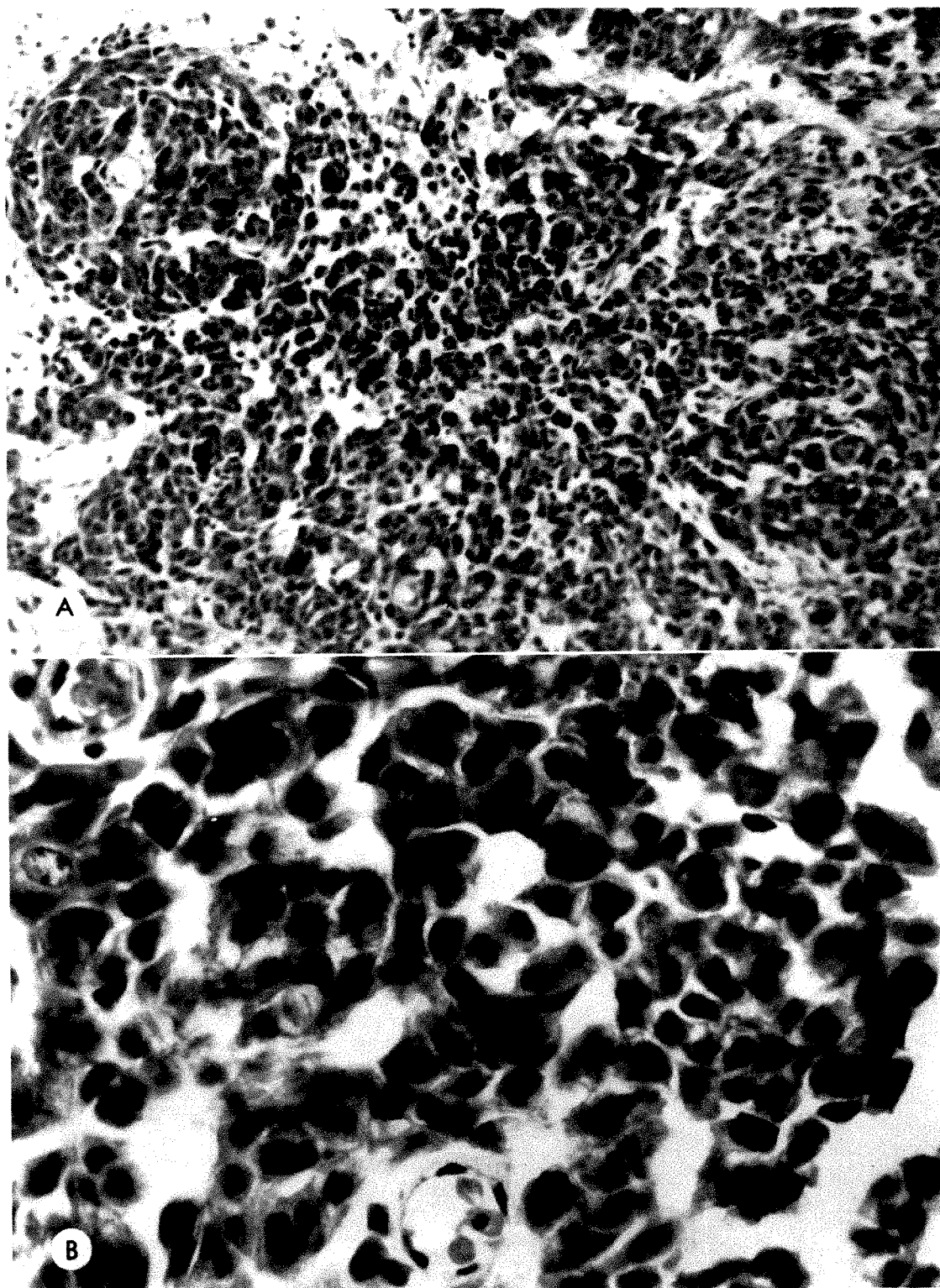


FIG. 3. Case 1. (*A* and *B*) Drill biopsy of lymph node mass prior to irradiation. *A* $\times 100$; *B* $\times 400$.

r in 15½ weeks. The mass diminished a little and became mobile over the next 6 months, but increased very slowly again over the next 30 months (Fig. 4).

Because of thinning of the epidermis and increase in projection, she was subjected to operation in November, 1958 removing the main mass and dissecting the lymph nodes up to the aortic bifurcation (Fig. 5, *A* and *B*). The uppermost lymph node was not involved. The wound required grafting which healed except for one small area which persisted unhealed for a month. Since then, she has had some lymphedema of the leg, and in August, 1964 a total abdominal hysterectomy for a fibroid uterus was performed, but no sign of recurrence was found in the lymph nodes up to the aortic chain and the liver was smooth.



FIG. 4. Case I. Clinical state 30 months after irradiation and prior to operation, showing pigmentation due to irradiation, subsidence of much of the mass and regrowth in central nodule.

CASE II. Female, aged 28 years. In 1940 the patient was treated by radium needle implantation elsewhere for a tumor about 5 cm. in diameter which had been growing for 12 months in the right scapular area. In August, 1943 she noted a swelling in the right supraclavicular fossa and in February, 1944 one in the right axilla. She was first seen in August, 1944 with a radiation scar in the skin of the posterior shoulder, a 5 cm. soft lymph node low on the medial wall of the right axilla, a further smaller, firmer lymph node posterosuperior to this, and a 3.5 cm. very soft lymph node in the right posterior supraclavicular area. Section of the original tumor was reported as probably a cutaneous angioma, but the material could not be located for review. Aspiration biopsy of the axillary mass on September 11, 1944 showed malignant melanoma (Fig. 6, *A* and *B*). There were no other clinical or roentgenologic signs of spread.

Through anterior, posterior and inferior fields, the axilla and supraclavicular region were irradiated using 200 kv., 20 ma., focus skin distance of 50 cm. and a filtration of 1.0 mm. Cu. Skin doses of 3,000 r, 3,000 r and 1,200 r, respectively, were given in 10 treatments from September 25, 1944 to October 31, 1944, amounting to a tumor dose of 4,000 r in the mid-axilla. Three months later the mass had subsided, but in order to supplement what was felt to be an inadequate dose, a volume implantation of radon needles into the axilla and supraclavicular region was carried out, delivering 8,000 r in 7 days to the center of the volume,

and 7,000 to 7,500 r in the same period at 0.5 cm. in the supraclavicular fossa. The radon needles were implanted on February 21, 1945 and removed on February 28, 1945 with a second degree reaction on the skin.

By November, 1945 she was having severe pain in the right arm and a tractotomy was performed as a palliative measure in December, 1945. Fluid collected in the supraclavicular fossa and was aspirated in May, 1947 but no melanogen or cells were detected. In August, 1947 she had a termination of pregnancy and subsequently a sterilization course of roentgen therapy. By 1950 a neuritis in the forearm and hand had led, through a period of discomfort, to anesthesia and trophic changes in the fingers with wasting and loss of movement. Radiation fibrosis restricted the movement of the shoulder. She failed to attend from 1951 until 1964 when she was referred because of mild thyrotoxicosis which was treated with 7 mc of radioiodine with good effect. A radionecrotic ulcer had appeared over the tip of the acromion and some necrotic bone was removed.

When last seen on April 14, 1965 she remained in good general health with a flail anesthetic arm which she refused to have amputated and a raw area on the posterior shoulder in the midst of dense fibrosis and telangiectasis. This showed some sign of healing (Fig. 7).

CASE III. Male, aged 31 years. In 1956 the patient reported with a 10 year history of a mole on the right calf which proved to be an ulcerated malignant melanoma, 2.5×2.5 cm. by 0.5 cm.

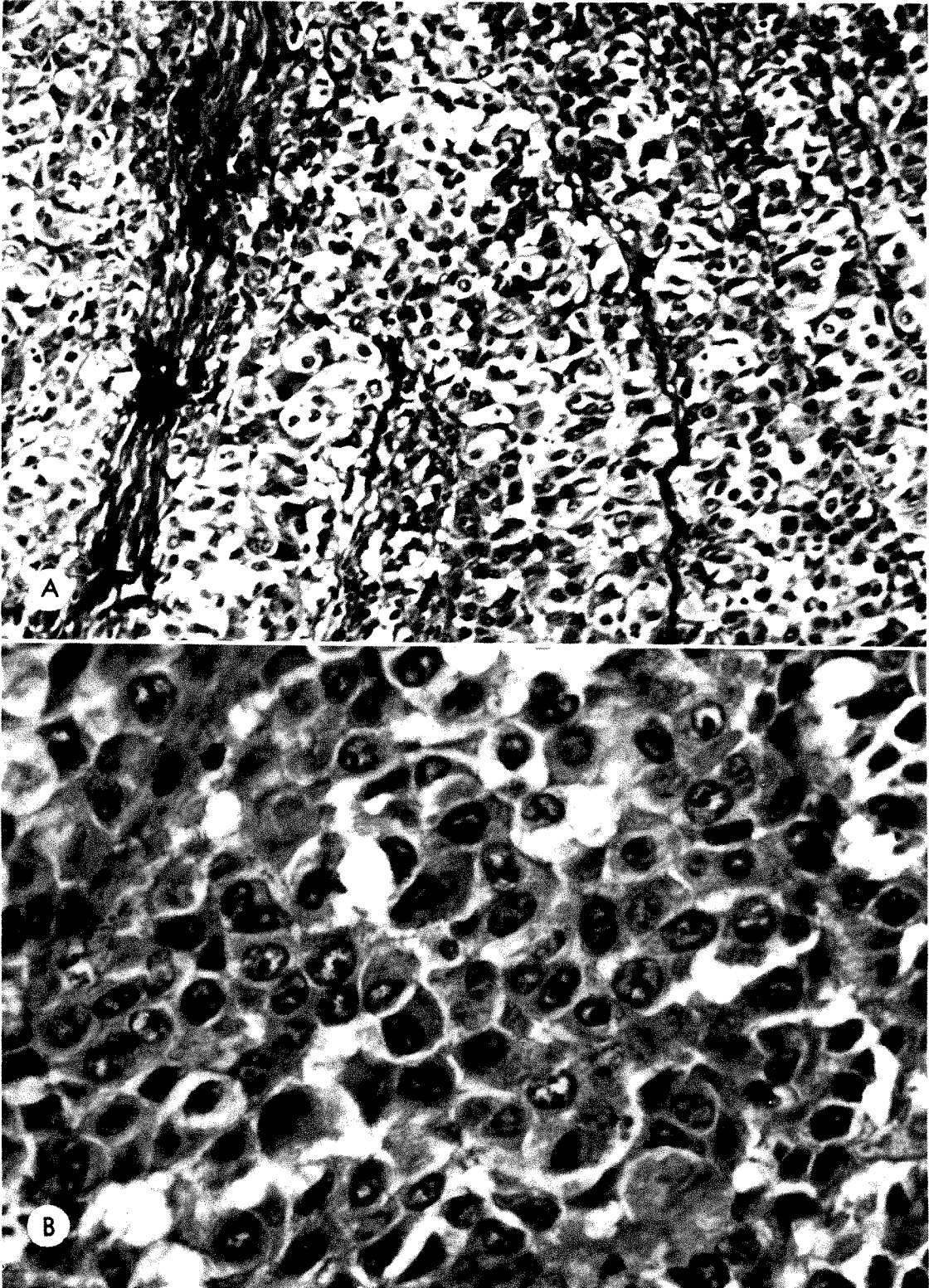


FIG. 5. Case 1. (*A* and *B*) Section of lymph nodes removed at surgery. *A* $\times 100$; *B* $\times 400$.

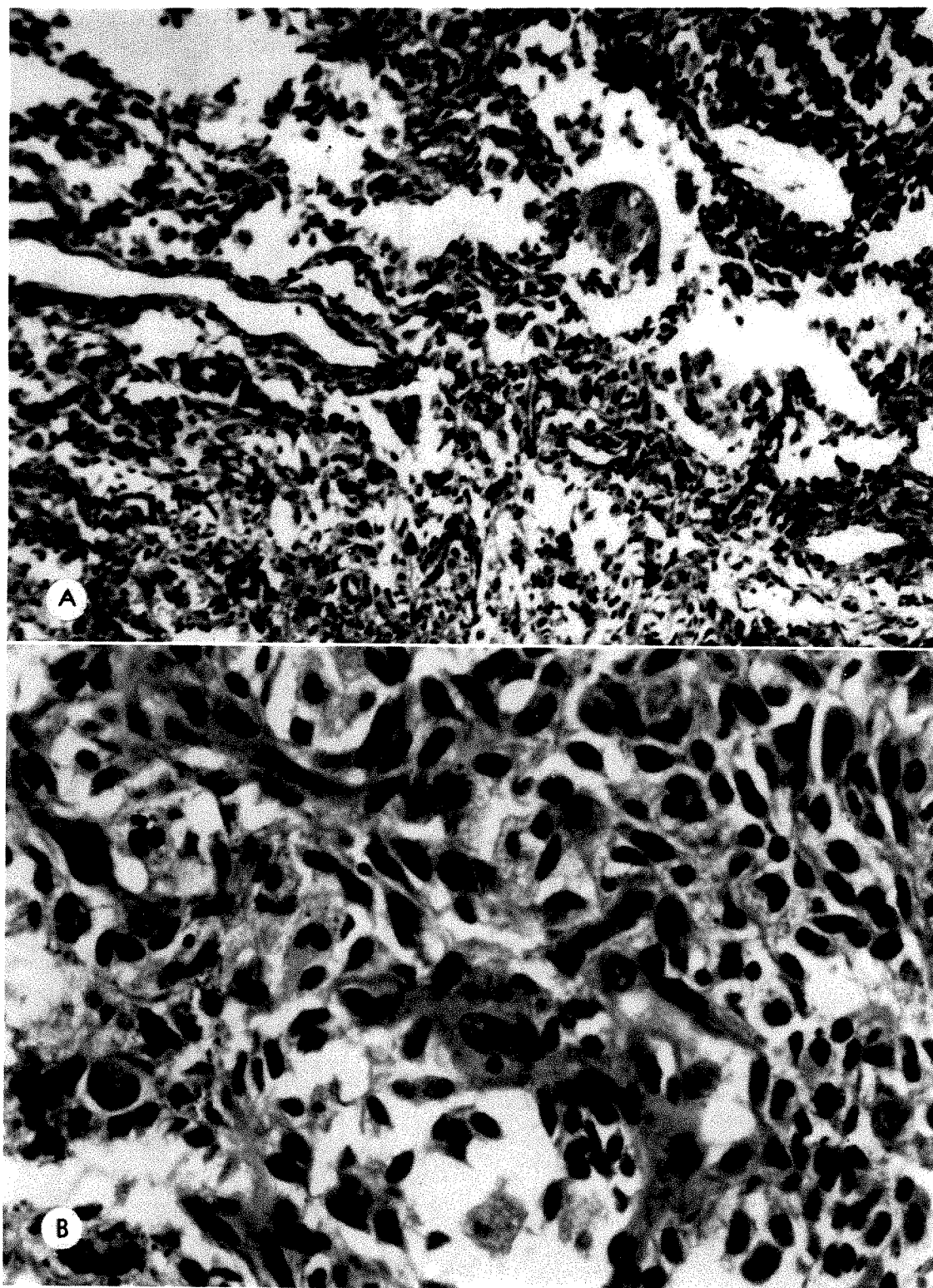


FIG. 6. Case 11. (*A* and *B*) Aspiration biopsy of axillary mass. *A* $\times 100$; *B* $\times 400$.



FIG. 7. Case 11. Radionecrosis of the shoulder and scarring in neck 20 years after heavy irradiation.

thick, with surrounding erythema 5.0 cm. in diameter. A firm mobile lymph node was found in the right inferomedial group of superficial inguinal lymph nodes, but no other evidence of extension was found. On November 1, 1956 wide excision of the calf lesion, en bloc dissection of the popliteal space which was free of tumor, and a complete block dissection of the femoral and inguinal lymph nodes to the common iliac bifurcation were carried out. The latter were found to be involved by melanoma (Fig. 8, *A* and *B*).

In August, 1959 he noted a lump in the opposite left groin and one in the right neck. Attempts at drill biopsy of the latter produced only muscle and fibrous tissue and a P^{32} uptake showed no increase over the affected areas. The lesions were observed over the next 6 months. By February, 1960 there were several 7 mm. nodules around the site of the primary lesion and one in the center of the skin graft. In the popliteal fossa the wound had broken down with a recurrent nodule at the edge of the sloughing ulcer. A skin nodule, 3.0 cm. in diameter, had appeared over the anterior superior iliac spine on the right, and the lymph nodes in the left groin were 3.0 cm. The neck lymph nodes were 3.5 cm., but the liver which had been intermittently palpable was not definitely enlarged. A test dose of 1,000 rads to a 5.0 cm. circular field over the skin nodule was given at a half value layer of 1.0 mm. Cu on February 16, 1960. By February 19, 1960, a reduction in size to 2.0 cm. was noted and therefore radiation therapy was started to the popliteal fossa in an attempt to heal the ulcer. Before the second dose of this

could be given, the patient complained of headache, became disorientated and drowsy and on March 9, 1960 a course of radiation therapy to the whole skull was started; 3,500 rads were given at the mid-point through the lateral ports, 20×15 cm., in 3 weeks using 4 mev. linear accelerator. This resulted in a slow interrupted recovery of cerebral function and by June he was considered normal mentally.

In the meantime, the lymph nodes in the left groin had grown to a 12×13 cm. mass and treatment was given to this area by a 15×15 cm. field anteriorly with a 4,000 rads peak dose in 9 increments from June 15, 1960 to July 4, 1960. By September the mass was only just palpable, the ulcer behind the knee had healed and the patient was able to go on a holiday.

On March 20, 1961 a subacute intestinal obstruction was treated conservatively but intermittent colicky pain persisted for 2 months. His general condition was improving when last seen in June, 1961, but he died of melanoma at home on July 3, 1961. The exact mode of death was not stated. His survival from the first treatment was 4 years 8 months, and from radiation treatment to the recurrences and brain metastases, 16 months.

SUMMARY

A study has been made of methods and results in the treatment of clinically significant lymph nodes in malignant melanoma. There was a cumulative 5 year survival of 27 per cent in the whole series including those patients who received no treatment. Surgery alone and radiotherapy alone as the first planned treatment policy resulted in the same figure. No untreated patient survived 5 years. Four of 10 patients in whom radiotherapy followed mainly local surgery survived and it is suggested that a trial should be made of pre-operative radiotherapy in cases with apparently only regional spread.

Peter MacCallum Clinic
481 Little Lonsdale Street
Melbourne, C.I., Australia

This work has been adapted from part of a thesis for Doctor of Medicine sustained by the University of Edinburgh in 1963. I would like to thank the Medical Director of the Peter MacCallum Clinic for permission to publish,

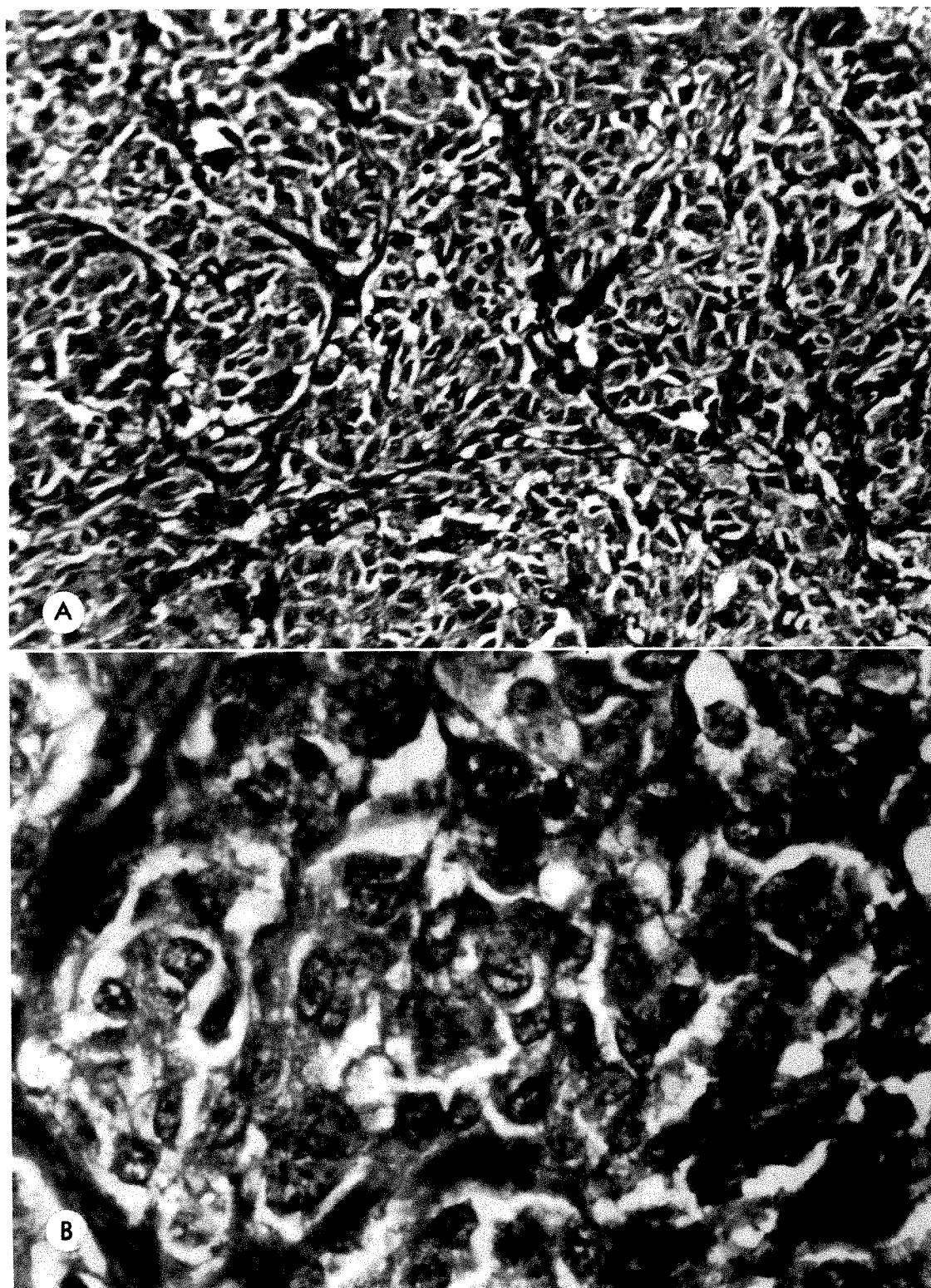


FIG. 8. Case III. (*A* and *B*) Section of lymph nodes from right groin. *A* $\times 100$; *B* $\times 400$.

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RESIDUAL RADIOPAQUE BOLUS IN MANAGING INTRASPINAL NEOPLASMS*

By CHARLES F. MARTIN, JR., M.D., EUGENE GEDGAUDAS, M.D., and GIULIO J. D'ANGIO, M.D.
MINNEAPOLIS, MINNESOTA

THE use of myelography in the diagnosis of neoplastic disease of the spinal cord and its associated structures is a universally recognized, standard technique. Perhaps less commonly appreciated is the value under certain circumstances of leaving a bolus of contrast material within the subarachnoid space at the completion of the study. In this way it is possible, for example, to facilitate frequent interval fluoroscopy and assess the response of a tumor as appropriate radiotherapy proceeds. Wood, Taveras and Pool²² gave such an example while discussing the general topic of myelography in relation to spinal cord metastasis from primary brain tumors. Two of these same authors more recently state,²¹ "In cases of medulloblastoma, the pantopaque may be left in place in the canal and re-examination performed following radiation therapy to demonstrate effects of treatment as well as the possibility of future recurrence of the lesion." This technique had been adopted independently by us in studying several patients, and we can attest to its usefulness as an adjunct in the management of patients with a variety of lesions related to the spinal cord.

INDICATIONS

Some indications for this procedure are as follows: (1) To permit frequent, direct visual evaluation of treatment response to radiation therapy in cases of intraspinal neoplasms. A current knowledge of the nature, extent, and response of a lesion to therapy is of great importance to the therapist in order that he may manage any particular case in an optimum manner. (2) To supplement neurologic examination in gaining a more complete evaluation of the clinical status of the patient with respect

to his intraspinal lesion. It is useful, for example, in infants and children where clinical evaluation often is difficult, or in patients in whom abnormal cord signs largely disappear with therapy but in whom the tumor persists and can still be seen as a smaller but nonetheless overt defect on myelography. (3) To assess the response of the tumor to treatment in patients with persistent neurologic symptoms from intraspinal tumors. The continuing presence of a mass calls for more therapy to relieve compression, whereas resolution of the tumor without change in signs denotes chronic damage from previous compression and contraindicates higher dose. (4) To demonstrate lesions at other levels when obstruction has been relieved. This is especially useful in patients with diseases that tend to form multiple nodules such as medulloblastoma. Some of these deposits can become quite large, yet remain clinically silent.⁹ (5) To allow better definition of dorsal lesions, especially in the thoracic area, by facilitating lateral supine decubitus roentgenography. These projections are otherwise often omitted because of difficulties in positioning occasioned by the continuing presence of the needle. (6) To monitor a therapeutic trial of irradiation in certain radiosensitive tumors causing early signs of cord compression rather than resorting immediately to laminectomy. (7) To achieve greater precision in dose prescription when radiation tolerance has been reduced by prior treatment and the smallest possible palliative dose is indicated.

PROCEDURE

Myelography is performed in the usual way. The contrast material commonly employed is ethyl iodophenylundecylate (io-

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From The Department of Radiology, University of Minnesota Hospitals, University of Minnesota Medical School, Minneapolis, Minnesota.

phenidylate, U.S.P., XVI), hereafter abbreviated as E.I.* If during myelography a lesion is found that will most likely require radiation therapy, residual contrast material is left in the subarachnoid space at the termination of the procedure. The amount to be left behind will vary with a number of factors, such as size of the subarachnoid space, nature of the lesion, level of the lesion, degree of obstruction, etc. Insufficient amounts will tend to give incomplete and confusing roentgenologic information. The minimum amount sufficient to be of future diagnostic help will be 4 to 6 cc. in the average adult; in the child, 2 to 3 cc. may suffice. Lesser amounts, however, can often be helpful as, for example, in the case of a complete block where the passage of even a small amount of contrast substance demonstrates restored continuity. At appropriate intervals during radiation therapy, fluoroscopy with indicated roentgenography of the subarachnoid space is performed as in myelography. During fluoroscopic observation, as much care as possible should be taken to prevent break-up of the column of E.I. into globules and to prevent spill into the intracranial subarachnoid space. When therapy has been terminated, the residual E.I. can well be removed if so desired; indeed, removal is recommended. (Of course, if there are signs of any significant reaction, the material should be removed earlier.)

PRECAUTIONS

Certain precautions should be taken in this procedure. A myelogram that is technically satisfactory is essential. To reduce the possibility of extradural leakage of contrast material, a needle preferably no larger than 19 gauge should be used. When the bolus has been deposited in the spinal subarachnoid space, the chance of losing E.I. into the intracranial subarachnoid compartment can be diminished by taking precautions in body and head position. For

example, the patient is urged to avoid bending over or performing similar maneuvers that would promote cephalad migration of the agent.

CONTRAINDICATIONS

The chief contraindication to leaving E.I. in the subarachnoid space would be any sign or symptom indicating sensitivity to the contrast material (*vide infra*). Another contraindication would be a valid history of iodine sensitivity. In the presence of acute or chronic arachnoiditis, the relative risks should be weighed carefully. Not only is satisfactory flow of the residual contrast material compromised, but its presence could aggravate the inflammatory process.

The following case history is presented in some detail to illustrate several of the points made above.

REPORT OF CASE

K.S. U.M.H. #1026136. This male was first seen at another hospital in March, 1964, at the age of 17 years. He had signs and symptoms consistent with a posterior fossa tumor. Craniotomy was performed and a medulloblastoma was removed from deep within the substance of the left cerebellar hemisphere. He was given postoperative irradiation to the posterior fossa and spinal subarachnoid space (250 kv. technique). The tumor dose given was estimated at 3,300 rads to the posterior fossa; and 2,225, 1,660, and 1,740 rads to the cervical, thoracic and lumbar levels of the spinal cord, respectively. His course was uneventful until October, 1964, when he had onset of back pain with radiation down the back of the left leg. Physical findings at that time were consistent with an intraspinal lesion involving nerve roots, S-2, 3, and 4.

A myelogram obtained on December 16, 1964, with 12 cc. of "pantopaque" showed a complete block at L-5, S-1 (Fig. 1). No other abnormalities were noted. The patient was treated with cobalt 60 teletherapy from December 30, 1964, to January 29, 1965, inclusive. A total tumor dose of 4,645 rads was given through a single posterior port, measuring $4 \times 8\frac{1}{2}$ cm. which included L-5 to S-3.

After the first few treatments, the patient's left leg discomfort disappeared and shortly his

* Marketed in the United States of America by Lafayette Pharmacal Co., Lafayette, Indiana, as "Pantopaque," and in England as "Myodil" (Glaxo).



FIG. 1. Myelogram made on December 16, 1964. Medulloblastoma metastasis. Complete block is present at L-5, S-1. Note symmetry at lower end of opaque column.

neurologic examination returned to normal. A small amount of "pantopaque" had been left in the subarachnoid space. Fluoroscopy with appropriate roentgenographic studies was performed approximately 3 times a week. On January 6, 1965, the subarachnoid block had partially opened. A similar study on January 16, 1965, showed further but incomplete resolution of the block. (In Figure 2A, the globules of "pantopaque" overlying S-1, 2 are residues from this examination.)

The patient's course was uneventful until April, 1965, when he developed left thigh and low back pain, right leg numbness and weakness, weakness in the left leg, numbness in the left face, inability to close the left eyelid, left tinnitus, and constipation. He soon developed urinary retention and became paraplegic. Neurologic examination elicited signs compat-

ible with posterior fossa recurrence and an intraspinal lesion at the thoracolumbar junction.

A myelogram on May 13, 1965, with 12 cc. of "pantopaque" revealed multiple subarachnoid deposits and complete blocks due to tumor at T-11 above and L-5, S-1 below (Fig. 2, A, B and C). The latter block was at the same level as the previous one demonstrated on December 16, 1964, but the contour at the distal end of the column had changed (compare Figures 1 and 2A). Approximately 4-5 cc. of "pantopaque" was left in the spinal subarachnoid space at the end of the procedure.

He was given cobalt 60 teletherapy from May 14 to June 8, 1965. A tumor dose of 3,400 rads was delivered to the entire cerebrospinal axis. From June 9 to June 11, 1965, he was given an additional 750 rads to the L-5, S-1 area in 3 treatments. Fluoroscopy and roentgenographic studies were performed using the residual bolus at appropriate intervals during the treatment period. Pertinent observations were made as follows.

On May 18, 1965, the blocks at T-11 and L-5, S-1 were little changed except in the latter area where there was filling out of the previous defect on the left, distally. Examination on May 20, 1965, revealed that the complete block at L-5, S-1 was partially resolved and "pantopaque" was now noted at the level of S-3. It also passed cephalad to T-11 due to partial resolution of tumor in this area (Fig. 3). On May 24, 1965, there was still more "pantopaque" below the level of L-5, S-1, and improved flow beyond T-11. The entire proximal spine up to and including the cervical area could now be studied with the same bolus, and no higher defect was found.

The patient gradually showed clinical improvement during the period of therapy and thereafter. On May 24, 1965, it was noted that he had recovered some movement in his legs, more on the left than on the right. He also had some urge to void. By June 7, 1965, it was noted that he had fair muscle power in both legs. Position sense was slightly decreased. Mild cerebellar dysfunction was present as manifested by adiadochokinesis of hands and feet, the right being greater than the left. Knee jerks were hyperactive bilaterally.

Fluoroscopy and roentgenographic study were continued. On June 1, 1965, free flow of bolus was noted throughout the subarachnoid

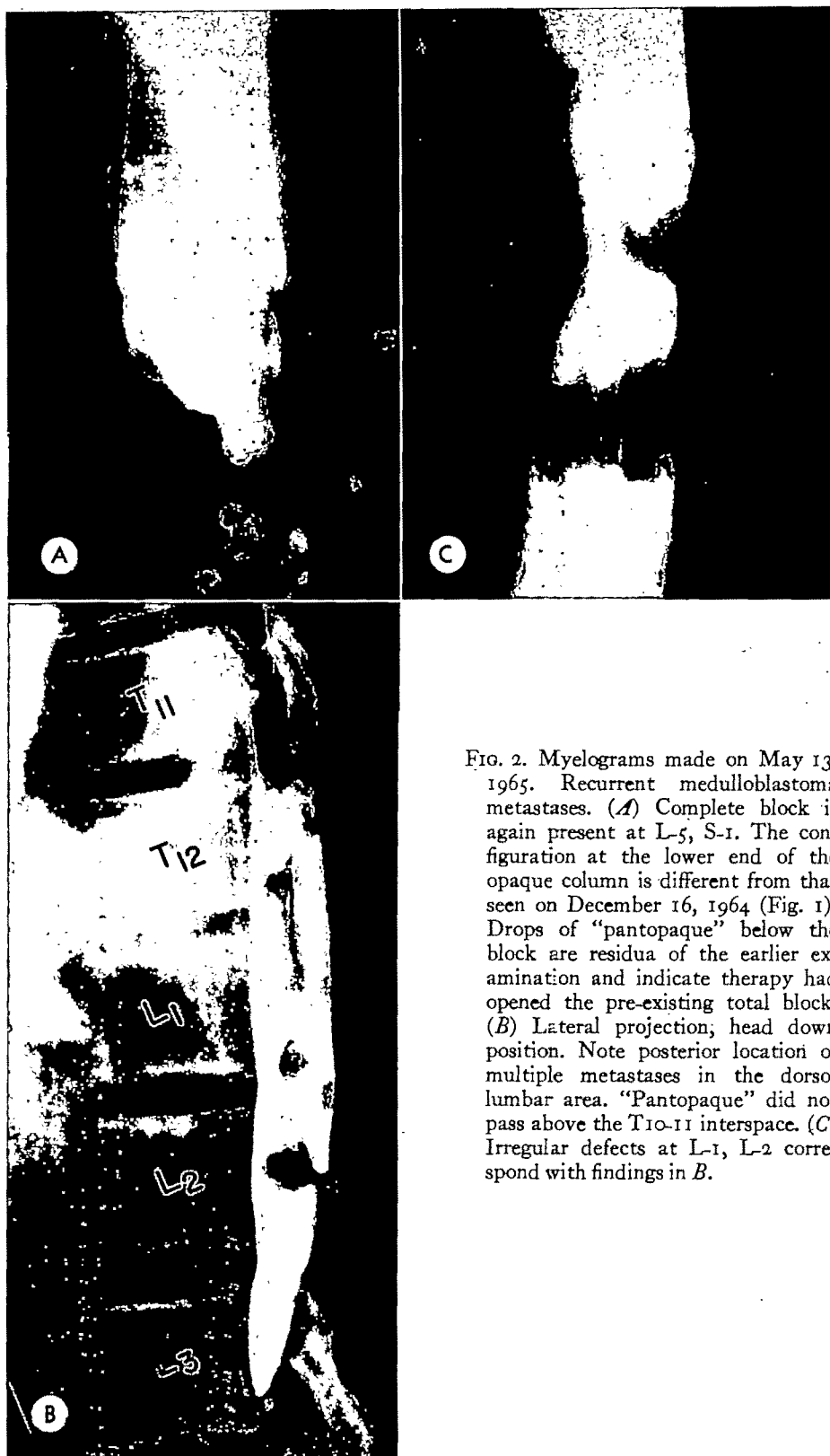


FIG. 2. Myelograms made on May 13, 1965. Recurrent medulloblastoma metastases. (A) Complete block is again present at L-5, S-1. The configuration at the lower end of the opaque column is different from that seen on December 16, 1964 (Fig. 1). Drops of "pantopaque" below the block are residua of the earlier examination and indicate therapy had opened the pre-existing total block. (B) Lateral projection, head down position. Note posterior location of multiple metastases in the dorso-lumbar area. "Pantopaque" did not pass above the T10-11 interspace. (C) Irregular defects at L-1, L-2 correspond with findings in B.



FIG. 3. Examination with residual bolus on May 20, 1965, one week after initiation of radiation therapy. There has been prompt response of the tumor with partial relief of the total block at T-11, documented by opaque matter now being seen above this level. Clinical improvement was noted by May 24, 1965.

space (Fig. 4). The appearance at L-5, S-1 did not change, but there was marked improvement of the earlier findings at the higher levels.

The examination was now considered normal except for the L-5, S-1 area. Because of the latter, and since the use of intrathecal radioactive gold 198 was contemplated, a new

myelogram was made on June 8, 1965, using 12 cc. of "pantopaque" to check for residual tumor. There was free flow of contrast material superiorly to the clivus. The myelogram was completely normal above the level of L-5, S-1 (Fig. 5, A and B). This study confirmed the normal findings of bolus myelography on June 1, 1965, and ruled out the presence of any mass. Seven cubic centimeters of "pantopaque" were left after the myelogram of June 8, 1965, to evaluate any change subsequent to further treatment which had been given to the L-5, S-1 area. Fluoroscopy and roentgenographic studies on June 14, 1965, showed no significant



FIG. 4. Examination with residual bolus on June 1, 1965. The column has fragmented but definite improvement at L-1, L-2 is visible. (Compare with Figure 2 C.) No residual tumor can be seen.

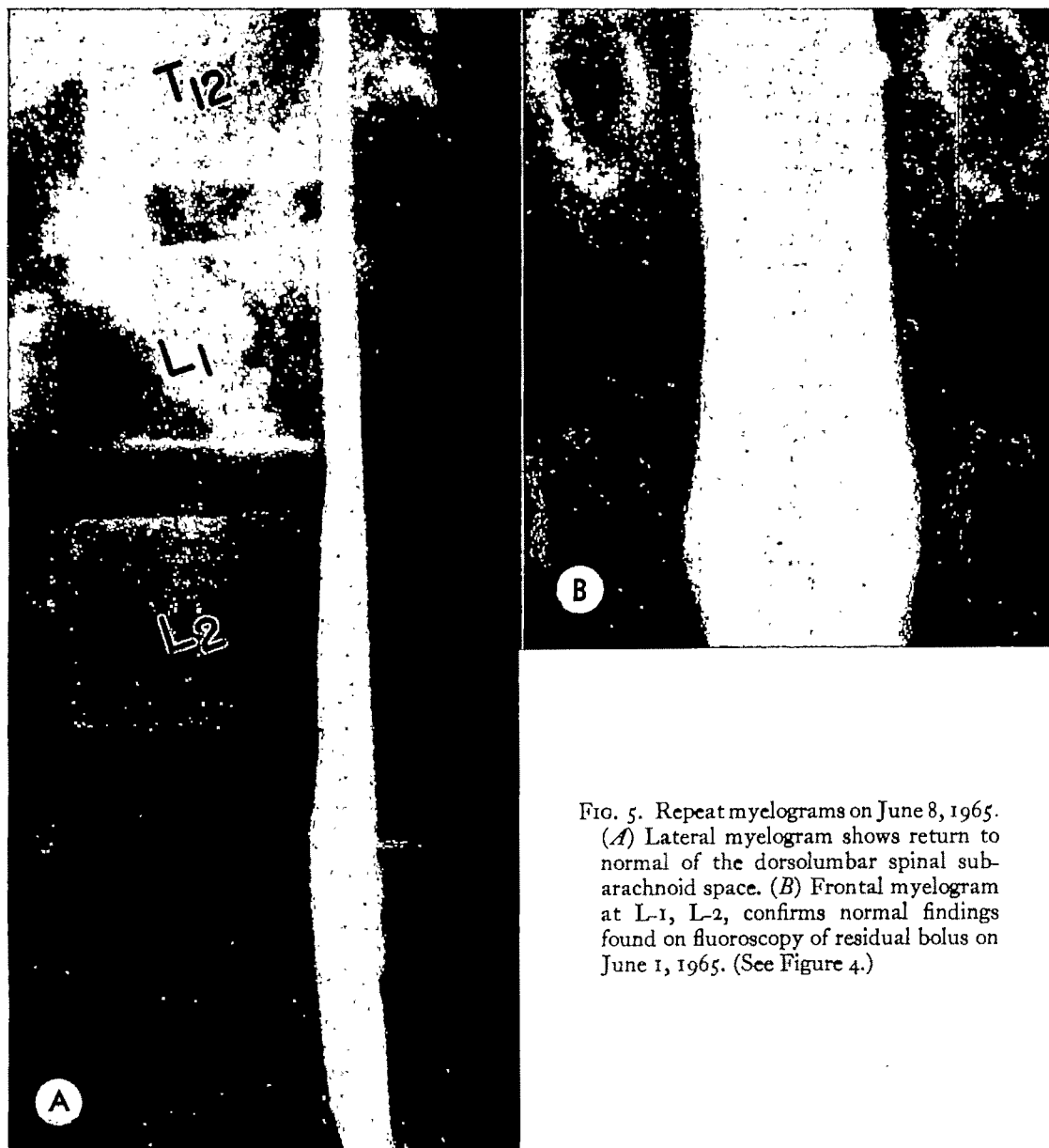


FIG. 5. Repeat myelograms on June 8, 1965. (A) Lateral myelogram shows return to normal of the dorsolumbar spinal subarachnoid space. (B) Frontal myelogram at L-1, L-2, confirms normal findings found on fluoroscopy of residual bolus on June 1, 1965. (See Figure 4.)

change. The abnormality at L-5, S-1 was attributed to arachnoiditis, persistent tumor or both. The residual "pantopaque" was removed on June 14, 1965.

To the date of this report (December, 1965), the patient has received 2 courses of radioactive gold intrathecally. A repeat myelogram in November, 1965, failed to show any recurrence of tumor.*

* A destructive focus in the right os pubis was identified in November, 1965, and bone marrow aspiration showed almost total replacement with tumor cells. He did not respond to

DISCUSSION

Some intracranial neoplasms have a propensity for dissemination via the cerebrospinal fluid and implantation along the spinal cord and its coverings. Most notable among such tumors are the medulloblas-

chemotherapeutic management for this complication, and expired March 20, 1966. Postmortem examination was restricted to the brain and spinal cord. No gross evidence of tumor was found in the brain, cord, or their coverings. Arachnoidal and meningeal thickening of the caudal end of these envelopes was present, in which inspissated "pantopaque" was trapped.

toma and the ependymoma, although other varieties, notably certain gliomas, have also been shown to follow the same route.^{2,4,14,18} Medulloblastoma is second to the astrocytoma amongst brain tumors in children and constitutes 25 per cent of the total.³ Ependymomas are found more frequently in children than in adults, making up approximately 7 per cent of intracranial tumors in younger patients.⁴ Metastatic implants often are multiple and occur at any level of the cord or cauda equina. They most generally appear as nodular masses, especially on the dorsal aspect of the cord and subarachnoid space.³ Sometimes, the implanted tumors spread as a sheath of tumor in the leptomeninges.^{2,21} The technique here described also lends itself to the assessment of radiation response of these neoplasms and such others as: (1) certain tumors primary in the spinal canal, such as ependymomas and astrocytomas; (2) extradural or intradural deposits; for example, those originating from carcinoma of the lung and breast, and similarly placed lymphomas; (3) direct extensions from metastatic sites in the vertebrae; and (4) direct extension from paraspinal tumors such as the neuroblastoma which commonly extends through the intervertebral foramina to the epidural space.

This technique avoids some of the difficulties inherent in repeated myelography, although the quality of the examination may not approach a study freshly carried out each time. However, myelography ordinarily cannot be performed satisfactorily more often than every 5-7 days because of so-called "collapse of the sac" after myelography. This interval is too long to wait in certain cases. Then, too, myelography is tedious for the patient and associated with unpleasant side effects (*e.g.*, headache). It can also prove costly, time-consuming, and technically difficult in some patients, such as children and the infirm.

HAZARDS

Leaving "pantopaque" (ethyl iodophenylundecylate [E.I.]) in the subarachnoid

space has been considered hazardous by some. It has been shown that this substance, when left in the spinal and intracranial subarachnoid space of experimental animals, can be irritating and lead to a proliferative meningeal reaction.^{10,17} Similar severe reactions have been reported in man. There are 2 reports of death attributed to E.I. reactions in the leptomeninges about the brain stem: (1) Erickson and van Baaren⁶ reported the demise of 1 of these patients due to intracranial arachnoiditis, the result of inadvertent introduction of E.I. into the basal cisterns during myelography 15 months before, and (2) Mason and Raaf¹² reported the second patient in whom an acute reaction, presumably to the E.I., occurred during the procedure. Five of the original 9 cc. of contrast substance were eventually removed but the patient died some 7 months after myelography. Postmortem examination revealed a diffuse aseptic meningitis that was attributed to E.I. hypersensitivity. Death was caused by brain stem compression. Davies,⁵ Hurteau, *et al.*,¹⁰ and Tarlov²⁰ reported severe adhesive arachnoiditis due to E.I., involving the cauda equina and lumbosacral leptomeninges. While it would seem clear that an occasional severe and even fatal reaction can occur with myelography, the experience of most investigators indicates that this is an eminently safe procedure. Thus, for example, in 2 large series of conventionally performed myelographies, 1,800 in one series reported by Shipp¹⁶ and 3,000 in another reported by Tainter and Grayson,¹⁹ no significant clinical complications were encountered. Transient, mild, meningeal reactions may occur.^{8,11,13,15} These are manifested chiefly as fever, headache, meningismus, malaise, and ileus. The cerebrospinal fluid may exhibit pleocytosis and elevated protein values.^{8,11,13,15} These findings generally are noted 6 to 24 hours after myelography and usually subside in a few days. Peacher and Robertson¹⁸ and Schnitkner and Booth¹⁵ found responses of this type to be more frequent when E.I. was left in the subarachnoid space, but the severity of the

reaction was not directly related to the amount of "pantopaque" left behind. Differing opinions stem from England, where it has been customary not to remove the contrast agent at the end of myelographic procedures. Davies⁵ stated that nearly 60 per cent of the patients in his series of 119 patients (125 myelographies) had post-myelographic reactions. The length of follow-up was 1-15 years. The average residual amount of E.I. was 5 cc. Of 70 reactors, 56 had immediate and 14 had chronic symptoms. In the former, the most common complaints were severe pain in the spine, headache, stiff neck, fever, and exacerbation of original symptoms. The most frequent chronic symptoms were headache, neck pain, severe backache, and continuous pain and cramps in the leg. Fixation of contrast material within the subarachnoid space was noted to occur in a few months to a year. Bering¹ studied 25 patients from under 6 months to 3 years after myelography. An average of 3 cc. of E.I. had been left in the canal. Only 1 patient had mild acute symptoms and there were no chronic symptoms attributed to the procedure. He found that the E.I. became fixed in a large conglomerate mass only once. Trapping of even small droplets was not seen before 2 months.

The allergic type reactions reported are generally attributed to individual sensitivity to E.I. or to the iodine fraction. It is well recognized that no satisfactory test has as yet been devised to predict severe reactions to iodine-containing contrast material.⁷ Indeed, it has been suggested that prior intradermal skin testing sensitizes patients. In 2 cases reported by Luce *et al.*,¹¹ myelography after skin testing resulted in a delayed meningeal reaction that had its onset roughly coincidental with a flare-up of the skin reaction at the skin test site.

Other infrequent complications of myelography are venous extravasation and pulmonary embolization of E.I.

We conclude that the risk of the procedure here described is low in patients with no history to suggest sensitivity to iodine

or other remarkable history of allergy. It is our opinion, therefore, that the advantages of this procedure outweigh hazards in patients with neoplastic diseases.

SUMMARY

Patients with intraspinal tumors often undergo myelographic examination. The subsequent course and response of such patients to radiation therapy can be documented expeditiously by leaving behind a bolus of the contrast agent at the time of the initial study. The technique is described in detail and illustrated with the report of a typical case. The indications, complications, and hazards are discussed.

Giulio J. D'Angio, M.D.
Department of Radiology
University of Minnesota Hospitals
Minneapolis, Minnesota 55455

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THYMIC AND SPLENIC IRRADIATION IN TREATMENT OF ACUTE LYMPHATIC LEUKEMIA*

By V. J. FISH, M.D.,†† H. S. WINCHELL, M.D.,‡ and J. H. LAWRENCE, M.D.‡
PALO ALTO, CALIFORNIA

THE thymus has been implicated as both the primordial source of lymphatic tissue as well as a possible site of humoral control of lymphatic tissue in fetal development.² Thymectomy has previously been demonstrated to be effective in suppressing the rate of spontaneous development of leukemia in the Ak and C57BL mouse.^{1,3,4} Because of the potential role of the thymus in control of lymphopoiesis, we instituted a protocol for thymic ablation by radiation, combined with splenic radiation, in the treatment of acute lymphatic leukemia of childhood and adolescence to determine whether such procedures would be of value in supplementing the management of these disorders by chemotherapy. Four patients were studied. Each of these patients received an estimated tissue dose of 3,000 rads to the thymus and 1,000 rads to the spleen, delivered within a 2 week period, using a telecobalt 60 unit.

During, and subsequent to, radiation therapy, chemical therapeutic agents were withheld until it was apparent that the patient was entering leukemic relapse.

In one patient treated during partial remission from drugs (Table I, P. N.), satisfactory remission without the need for chemotherapeutic agents was obtained for an 8 month period following thymic and

splenic irradiation. The patient's subsequent course was complicated by spontaneous abortion and septicemia. In 3 additional patients (J. P. R., 5 year old male; R. S., 23/4 year old male; and P. F. R., 5 year old male), radiation therapy was initiated following prolonged remissions with the usual chemotherapeutic agents and at a time when the patient's leukemic process was judged on the basis of bone marrow biopsy to be relatively resistant to chemotherapy. Following therapy in 2 of these cases, the patients had some objective improvement in the leukemic process, but the improvement was short-lived, with progressive relapse occurring within 2 to 3 months following the completion of radiation therapy. Both patients subsequently appeared to have a somewhat improved response of their leukemic process to chemotherapeutic agents. However, their course was not sufficiently distinct from patients treated without thymic or splenic radiation to establish definite benefit of this therapeutic regimen.

SUMMARY

Table I shows the time elapsed between the completion of radiation therapy to the thymus and spleen, the time of reinstitution of drugs and the patient's time of

TABLE I

Patient	Age (yr.)	Sex	Date of Diagnosis	Dates of Radiation Therapy	Date of Relapse	Date of Death	Remarks
P.N.	19	F	Feb., 1963	May 6-18, 1963	Jan. 8, 1964	Feb. 28, 1964	Radiation remission 8 months
R.S.	24	M	Aug., 1963	Jan. 7-24, 1964	Apr. 14, 1964	Sept. 14, 1964	Radiation remission 3 months
P.F.R.	5	M	Nov., 1962	Feb. 6-19, 1964	Apr. 15, 1964	July 23, 1964	Radiation remission 2 months
J.P.R.	5	M	Sept., 1962	June 1-12, 1964	—	Sept. 9, 1964	No definite radiation remission (radiation therapy not completed because of white blood cell count drop below 2,000)

* From the Department of Radiology, Palo Alto Medical Clinic, Palo Alto, California,† and the Donner Laboratory, University of California, Berkeley, California.‡

death. From this it can be deduced that only one patient (P. N.) had definite therapeutic benefit from radiation therapy to thymus and spleen.

V. J. Fish, M.D.
300 Homer Avenue
Palo Alto, California 94301

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THE EFFECT OF COMBINED RADIATION AND ACTINOMYCIN D THERAPY ON INCOMPLETELY REMOVED MOUSE TUMORS*

By MELVIN TEFFT, M.D., BARBARA L. BROWN, B.A., CHARLOTTE L. MADDOCK,
M.D., and GIULIO J. D'ANGIO, M.D.†
BOSTON, MASSACHUSETTS

THE fact that actinomycin D, when combined with irradiation, increases injury both to normal and to neoplastic tissue has been studied by many methods.^{1,3,4,5,6,7,9,12,21} This combined therapy, however, to an area from which tumor has been incompletely removed by surgical means has, to our knowledge, not been explored. Since surgical eradication of tumor is frequently incomplete, a question arises whether this procedure should, therefore, be followed by treatment with roentgen radiation; with a chemotherapeutic agent, especially one that may improve the effect of irradiation; or by a combination of both. This is a dilemma that concerns the surgeon. Our investigation was designed to elucidate further this problem in an experimental situation where such therapy could be administered under rigidly controlled conditions.

MATERIALS AND METHODS

The Ridgway osteogenic sarcoma, which has been extensively explored in these laboratories, provided a convenient tool for this purpose. This tumor, originally described by Moore¹⁵ in 1951 and classified then as an osteogenic sarcoma, but which promptly lost any characteristics of such a neoplasm,¹⁹ is currently regarded as an undifferentiated non-metastasizing round-cell tumor. Both roentgen therapy and actinomycin D cause a reduction in the growth rate of the tumor.^{5,20} It is maintained for transplantation purposes by subcutaneous trochar implantation in the

AKR mouse; however, in the present experiments, heavy cell suspensions were implanted subcutaneously into the AKR female $\times$ DBA/2 male hybrid (AKD₂F₁).

In a small preliminary experiment, the results hoped for were achieved in these mice. Surgery plus combined roentgen ray and actinomycin D treatment had afforded a significantly longer survival time ($P = 0.025$), and, at death or sacrifice, a few mice presented without recurrent tumor. An attempt was made, therefore, to repeat this study with larger numbers of mice and two additional experiments were then undertaken.

EXPERIMENT I

Eighty-five male AKD₂F₁ mice were implanted subcutaneously with tumor suspension in the right hind leg. Because of inequalities in the growth of the tumor, the mice were divided into 4 groups. In Group A, when the tumors in all groups achieved a mean size of 1.82 to 1.83 cm. sq., 18 days after implantation in mice weighing from 25 to 33 gm., 30 mice were selected for experimentation, 6 per category. In Group B, 22 days after implantation the mean sizes of tumors varied from 1.04 to 1.22 cm. sq. and the mouse weights from 27 to 32 gm., and 5 mice were selected for each of the same categories, making a total of 25. In Group C, 28 days after implantation the mean sizes of tumors varied from 1.27 to 1.3 cm. sq. and the mouse weights from 27 to 30 grams; 3 mice were available for each

* From The Children's Cancer Research Foundation, The Children's Hospital Medical Center, and Harvard Medical School, Boston, Massachusetts.

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† Present Address: University of Minnesota Hospitals, Minneapolis, Minnesota.

TABLE I

MEAN TUMOR GROWTH RATES AND MEAN SURVIVAL TIMES OF MICE AFTER SURGICAL EXCISION
OF TUMOR FOLLOWED BY CHEMOTHERAPY, ROENTGEN AND COMBINED THERAPY*

EXPERIMENT 1

Group	Category	Mean Tumor Growth Rate		Mean Survival		Range (days)	100 Day Survival without Tumor (survival/total no.)
		(cm. ³ /day)	S.D.**	(days)	S.D.**		
1*	Controls—no treatment	0.39	0.0048	15.6	5.5	5-21	0/17
2	Controls—surgery	0.36	0.0049	16.7	8.0	4-33	0/17
3	Actinomycin D	0.35	0.0031	25.2	24.9	14-42	0/16
4	Roentgen Therapy	0.27	0.0042	45.9	12.4	28-68	0/15
5	Combined Therapy	0.12	0.0033	63.6	21.9	42-110	2/17

* Tumor used was Ridgway osteogenic sarcoma; strain of mice, AKD2F1; chemotherapy, actinomycin D at 150 µg./kg., i.p.×1, and roentgen therapy at 1,500 r×1.

** Standard deviation was calculated by the formula: $SD = \sqrt{\frac{(\bar{X} - X)^2}{n}}$.

of the same categories, thus adding 15 more mice. The number of mice in Group D was 15, divided equally into 5 categories. The time interval was 31 days, mean tumor sizes ranged from 1.04 to 1.08 cm. sq. and the mouse weights from 30 to 35 gm. The termination date was established at 110 days.

The categories in all the groups were as follows: (1) controls—no treatment; (2) controls—surgical excision of tumor; (3) surgical excision of tumor plus actinomycin D, given once in a dose of 150 µg./kg.; (4) surgical excision of tumor, plus roentgen therapy in a dose of 1,500 r given once; and

(5) surgical excision of tumor plus a combination of the 2 modalities described in (3) and (4).

Nembutal, in a dose of 0.01 mg./gm. of body weight given intraperitoneally, was employed for anesthesia. After the application of iodine, followed by alcohol, the skin over the tumor, as well as the tumor capsule, was incised, and the tumor was shelled out. Since this tumor is not completely invested by a capsule, such a procedure always leaves tumor cells behind. Skin closure by suturing followed. There was little loss of blood.

TABLE II

MEAN TUMOR GROWTH RATES AND MEAN SURVIVAL TIMES OF MICE AFTER SURGICAL EXCISION
OF TUMOR FOLLOWED BY CHEMOTHERAPY, ROENTGEN AND COMBINED THERAPY*

EXPERIMENT 2

Group	Category	Mean Tumor Growth Rate		Mean Survival		Range (days)	100 Day Survival without Tumor (survival/total no.)
		(cm. ³ /day)	S.D.**	(days)	S.D.**		
1*	Controls—no treatment	0.32	0.0056	17.8	3.17	13-23	0/15
2	Controls—surgery	0.30	0.0078	14.3	3.16	10-21	0/15
3	Actinomycin D	0.22	0.0057	32.9	5.51	21-42	0/15
4	Roentgen Therapy	0.23	0.0069	42.3	13.06	20-26	0/15
5	Combined Therapy	0.16	0.0111	60.2	18.91	31-147	2/15

* The same tumor system, strain of mice, sex, and doses of actinomycin D and roentgen therapy used as in Table I.

** SD—as in Table I.

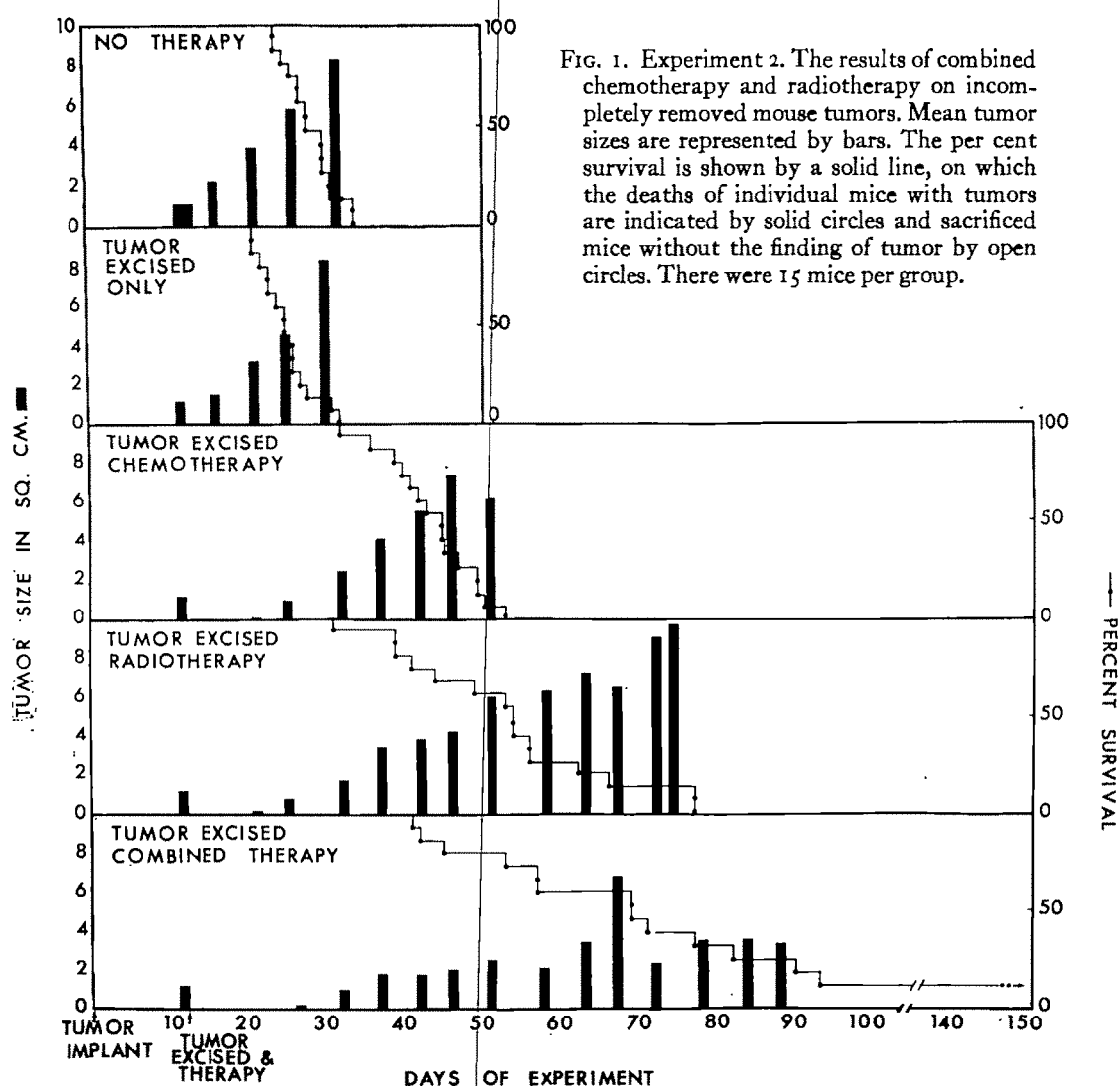


FIG. 1. Experiment 2. The results of combined chemotherapy and radiotherapy on incompletely removed mouse tumors. Mean tumor sizes are represented by bars. The per cent survival is shown by a solid line, on which the deaths of individual mice with tumors are indicated by solid circles and sacrificed mice without the finding of tumor by open circles. There were 15 mice per group.

Treatment followed in the groups as designated and was complete within an hour after operation. The hind legs of mice in Categories 4 and 5 were appropriately shielded from back-scatter by 3 mm. of lead and were subjected to 1,500 r as measured in air. Irradiation factors were 250 kvp., 15 ma., 1 mm. Al filter for a half value layer of 0.7 mm. Cu and a 40 cm. target skin distance. In the categories designated for combined therapy, the administration of actinomycin D immediately preceded irradiation.

Tumors were measured in 2 dimensions 3 times weekly, and body weights were measured on the same occasions. The final tumor measurements and weights were

noted. All the mice were studied until death or sacrifice.

Six mice were initially included in every category of Group A but apparently because of shock from surgical trauma and because of additional factors possibly related to therapy, 1 mouse in Category 3 and 2 in Category 4 died 24 to 48 hours after surgery, before regrowth of tumor could have occurred; hence, they were omitted from the data of these categories.

EXPERIMENT 2

This experiment differed from the previous one in the time interval between implantation date and surgery, which here

TABLE III
STATISTICAL COMPARISONS OF MEAN SURVIVAL TIMES OF VARIOUS CATEGORIES
EXPERIMENT I

	t Value	p Value	Significance
Controls <i>vs.</i> Surgical Controls	0.429	>0.500	Not significant
Surgical Controls <i>vs.</i> Actinomycin D	1.816	Between 0.100 and 0.050	Not significant
Surgical Controls <i>vs.</i> Roentgen Therapy	7.798	<0.001	Highly significant
Surgical Controls <i>vs.</i> Combined Therapy	9.267	<0.001	Highly significant
Actinomycin D <i>vs.</i> Combined Therapy	4.533	<0.001	Highly significant
Roentgen Therapy <i>vs.</i> Combined Therapy	2.639	Between 0.025 and 0.010	Significant

was 11 days; in the initial mean tumor size, which was 1.22 cm. sq.; in the initial mean weights of mice, which were 25 to 27 gm.; in the number allotted to the various categories, which was 14 in every group; and in the termination date, which was 147 days. Procedures were otherwise similar.

RESULTS

Experiments 1A to 1D, because of the small numbers of mice in all the categories, are considered together and analyzed statistically as one.

The results of both experiments are shown in Tables I and II. These show: mean tumor growth rate, defined as final tumor size minus initial tumor size in square centimeters divided by the number of days of survival; mean survival time in days; range in days; and the number of mice surviving beyond 100 days without tumor related to the total number. In Figure 1, the results of Experiment 2 are graphically presented.

In Tables III, IV, V and VI, statistical comparisons in both experiments are made

of survival times and tumor growth rates, giving *t* and *p* values,¹⁸ and their significance. The 6 categories which are compared are: (1) controls *vs.* surgical controls; (2) surgical controls *vs.* actinomycin D; (3) surgical controls *vs.* roentgen therapy; (4) surgical controls *vs.* combined therapy; (5) actinomycin D *vs.* combined therapy; and (6) roentgen therapy *vs.* combined therapy.

The results indicate that *surgical removal* of the tumor does not either prolong survival time or reduce tumor growth rate. In fact, in Experiment 1, a shortened mean survival time was noted, a not unexpected outcome that might be due to surgical trauma. Actinomycin D added to surgery produced in both experiments a variable effect as measured by the two parameters employed; survival time was not significantly better in Experiment 1, but was significantly better in Experiment 2. Roentgen therapy administered after surgery always resulted in improved mean survival times. However, tumor growth rate was significantly affected only in Experiment 2.

TABLE IV
STATISTICAL COMPARISONS OF MEAN GROWTH RATES OF VARIOUS CATEGORIES
EXPERIMENT I

	t Value	p Value	Significance
Controls <i>vs.</i> Surgical Controls	0.411	>0.50	Not significant
Surgical Controls <i>vs.</i> Actinomycin D	0.212	>0.50	Not significant
Surgical Controls <i>vs.</i> Roentgen Therapy	1.823	Between 0.100 and 0.050	Not significant
Surgical Controls <i>vs.</i> Combined Therapy	5.185	<0.001	Highly significant
Actinomycin D <i>vs.</i> Combined Therapy	6.368	<0.001	Highly significant
Roentgen Therapy <i>vs.</i> Combined Therapy	3.456	Between 0.005 and 0.001	Significant

TABLE V

STATISTICAL COMPARISONS OF MEAN SURVIVAL TIMES OF VARIOUS CATEGORIES
EXPERIMENT 2

	t Value	p Value	Significance
Control <i>vs.</i> Surgical Controls	2.8906	Between 0.010 and 0.005	Significant
Surgical Controls <i>vs.</i> Actinomycin D	10.8421	<0.001	Highly significant
Surgical Control <i>vs.</i> Roentgen Therapy	7.7756	<0.001	Highly significant
Surgical Controls <i>vs.</i> Combined Therapy	8.9708	<0.001	Highly significant
Actinomycin D <i>vs.</i> Combined Therapy	5.2537	<0.001	Highly significant
Roentgen Therapy <i>vs.</i> Combined Therapy	2.9247	Between 0.010 and 0.005	Significant

Surgery plus the combined therapy afforded a significant improvement over surgery plus either one of the two modalities employed in both Experiments 1 and 2, but deceleration of tumor growth rate, when these two categories were compared, was significantly greater only in Experiment 1. In all situations, the combined therapy added to surgery produced significantly better results than surgery alone.

DISCUSSION

The investigation here reported provides no explanation of the mechanism of the effect of roentgen rays and actinomycin D used in combination. Attempts to define this mechanism have received the attention of other workers,^{1,2,6} and can undoubtedly be better assessed in simpler systems.^{2,6,8-12,14,16,17} In this investigation, attempts were made only to find out whether the results of surgical excision of a tumor could be improved by following surgery with roentgen therapy or with a chemotherapeutic agent, and whether the combination of

these two modalities after surgery would result in a better effect. Since 100 day survivals without tumor were noted in this experimental situation only when surgical removal was followed by the combined treatment, it appears that complete elimination of the tumor is achieved only in this way.

The investigation, of course, suffers from the fact that no quantitative assessment of the numbers of viable cells remaining after operation is possible. It does, however, fairly closely mimic comparable clinical situations and may, therefore, suggest the use of added treatment in a limited number of human neoplasms excised surgically.

SUMMARY

In an experimental situation, *viz.*, excised ROS in the AKD2F1 mouse, simulating incomplete surgical removal of tumor, it was shown that roentgen therapy at 1,500 r and actinomycin D at 150 μ g./kg., both applied once, very significantly improved

TABLE VI

STATISTICAL COMPARISONS OF MEAN GROWTH RATES OF VARIOUS CATEGORIES
EXPERIMENT 2

	t Value	p Value	Significance
Controls <i>vs.</i> Surgical Controls	0.6976	>0.50	Not significant
Surgical Controls <i>vs.</i> Actinomycin D	3.2046	Between 0.005 and 0.001	Significant
Surgical Controls <i>vs.</i> Roentgen Therapy	2.5650	Between 0.025 and 0.010	Significant
Surgical Controls <i>vs.</i> Combined Therapy	3.8350	<0.001	Highly significant
Actinomycin D <i>vs.</i> Combined Therapy	1.7342	Between 0.100 and 0.050	Not significant
Roentgen Therapy <i>vs.</i> Combined Therapy	1.9607	Between 0.050 and 0.025	Borderline

the outcome, as compared to surgery alone. Results were measured by two parameters, *i.e.*, survival time and tumor growth rate. When survival times were compared, surgery followed by combined therapy always produced results superior to those obtained by surgery followed by either modality; however, when tumor growth rates were assessed, only in the first experiment were better results obtained, when combined therapy was used after surgery.

Melvin Tefft, M.D.

The Children's Hospital Medical Center
300 Longwood Avenue
Boston, Massachusetts 02115

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THE RADIOPROTECTIVE AND ANTI-TUMOR EFFECT OF MIXED BACTERIAL TOXINS AND ANTHRAMYCIN*

By DONALD R. COLE, M.D., F.A.C.S., BRENDA B. DREYER, B.S.,† LOUIS M. ROUSSELOT, M.D., F.A.C.S., and MOSES D. TENDLER, Ph.D.‡
NEW YORK, NEW YORK

DURING the past decade there have been numerous publications attesting to the effectiveness of various microbial products in protecting animals against lethal irradiation. Protection has been elicited by extracts from several organisms and several complex polysaccharide materials of microbial origin: *Brucella melitensis*,^{2,8,19} *Proteus morganii*,^{2,3,4} *Pseudomonas aeruginosa*,¹⁷ *Salmonella typhosa*,^{2,12,16,17,18} *Salmonella typhimurium*,⁸ *Serratia marcescens* mixed with *Streptococcus pyogenes*,¹ *streptococcus* alone,¹⁷ dextran,^{7,8} and zymosan.^{2,14,16,18,22}

Anthracyclin is a fermentation product derived from a thermophilic streptomycete. In animal studies^{12,21} and clinical evaluation,¹⁰ an anti-tumor effect has been demonstrated without leukopenia or thrombopenia, but occasionally leukocytosis and (in rabbits) thrombocytosis. This study was undertaken to determine the effect of anthracyclin or mixed bacterial toxins (M.B.T.) combined with irradiation.

MATERIALS AND METHODS

The antibiotic, anthracyclin, was prepared from a strain of *Streptomyces thermophilum* by the classic fermentation technique described by Tendler and Burkholder.²⁰ Purification of this product and an attempt to isolate and characterize the substances responsible for anti-tumor effect resulted in a number of fractions isolated from the fermentation broth. The compound identified as anthracyclin is labeled

B, C, D and K according to the fraction tested. The empirical formula for the pure crystalline methyl of anthracyclin coded as /15 has recently been developed and is $C_{17}H_{19}N_2O_4 \cdot H_2O$. A therapeutic dose of anthracyclin* was administered intramuscularly to mice and by the intramuscular, intravenous or oral route in humans.

A bacterial mixture of heat killed cultures of *Streptococcus pyogenes* and *Serratia marcescens*, mixed bacterial toxins (M.B.T.) was prepared according to the method of Johnston *et al.*¹¹ A therapeutic dose, 0.1 ml. or 0.05 ml., of the undiluted bacterial preparation was injected intravenously into mice.

LABORATORY EXPERIMENTS

The basic plan consisted of injecting mice with anthracyclin or M.B.T. prior to lethal irradiation and recording the survival time and 30 day mortality; *i.e.*, studying the efficacy of each as a protectant against irradiation mortality in mice. Control mice receiving saline injections were included in the study. Swiss albino male mice, 25–30 gm. of weight, 60–90 days of age were used. Total body irradiation of 600 r, 700 r or 1,000 r was delivered 24 hours following injection of the anthracyclin or M.B.T. The 24 hour interval between injection and irradiation was chosen since this time interval had proven most effective in the screen-

* Anthracyclin as used in the body of this paper will refer to the pure crystalline product as described above (anthracyclin 15) as well as various other, less pure fractions.

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† Oliver E. Spencer Fellow in Cancer Research, 1963–1966.

‡ Department of Biology, Yeshiva University, New York, New York.

TABLE I
MORTALITY AND SURVIVAL OF MICE TREATED WITH M.B.T. OR ANTHRAMYCIN
24 HOURS PRIOR TO IRRADIATION WITH 600 R

Bacterial or Fungal Product	Drug Dosage	No. of Mice Screened	30 Day Mortality	Per Cent Mortality	Mean Survival (days)
M.B.T.	0.05 cc.	20	0/20	0	30
Anthracycin/2 (5886)	0.5 mg.	25	13/25	50	15-30
Anthracycin/12 (C6030A)	(100 units)				
	0.01 mg.	20	4/20	20	18-30
Anthracycin/15 (C6124)	(100 units)	20	0/20	0	30
Saline	0.05 cc.	20	10/20	50	16-30

ing of other antigens. Irradiation was delivered from a Siemens 250 kv. roentgen-ray therapy machine operated at 200 kv., 14.8 ma. and a distance of 50 cm. Added filtration consisted of 0.5 mm. Cu and a half value layer of 1.3 cm. Al. The animals were kept in a temperature controlled room and fed tap water and Purina Lab Chow *ad libitum*. The mice were caged (10/cage) and death checks were made once a day for 30 days following inoculation.

RESULTS

Our results seem to indicate increased host resistance to irradiation when M.B.T. or anthramycin is injected prior to radiation exposure.

A single dose of M.B.T. appears to afford complete protection to mice against 600 r irradiation when injected 24 hours prior to roentgen-ray therapy. The pure anthramycin completely protected the mice subjected to 600 r of irradiation, whereas the

TABLE II
MORTALITY AND SURVIVAL OF MICE TREATED WITH M.B.T. OR ANTHRAMYCIN
24 HOURS PRIOR TO IRRADIATION WITH 700 R

Bacterial or Fungal Product	Drug Dosage	No. of Mice Screened	30 Day Mortality	Per Cent Mortality	Mean Survival (days)
M.B.T.	0.05 cc.	60	5/60	8	30
Anthracycin (5585)	2.5 mg.	25	25/25	100	1-3
Anthracycin	5.0 mg.	25	25/25	100	1-3
Anthracycin	7.5 mg.	25	25/25	100	1-3
Anthracycin/2 (5845)	2.5 mg.	25	0/25	0	30
Anthracycin/2	5.0 mg.	25	0/25	0	30
Anthracycin/2	7.5 mg.	25	0/25	0	30
Anthracycin/2 (5886)	2.5 mg.	25	6/25	24	12
Anthracycin/2	5.0 mg.	25	10/25	40	11-12
Anthracycin/2	0.5 mg.	25	13/25	52	12-24
Anthracycin/2 (5935)	0.5 mg.	25	8/25	32	5-16
Anthracycin/12	0.05 mg.	25	24/25	96	10-28
Anthracycin/12	0.04 mg.	25	25/25	100	8-14
Anthracycin/12	0.02 mg.	25	13/25	52	6-20
Anthracycin/12	0.01 mg.	24	5/16	31	15-21
Anthracycin/12	0.004 mg.	25	24/25	96	5-21
Anthracycin/15 (C6124)	(30 units)	10	3/10	30	3-16
Anthracycin/15	(100 units)	20	8/20	40	3-12
Saline	0.05 cc.	40	36/40	90	9-19

TABLE III
MORTALITY AND SURVIVAL OF MICE TREATED WITH M.B.T. OR ANTHRAMYCIN
24 HOURS PRIOR TO IRRADIATION WITH 1,000 R

Bacterial or Fungal Product	Drug Dosage	No. of Mice Screened	30 Day Mortality	Per Cent Mortality	Mean Survival (days)
M.B.T.	0.05 cc.	20	20/20	100	6-10
Anthramycin/II (D)	2.0 mg.	20	20/20	100	2-8
Anthramycin/II	10 mg.	10	10/10	100	3-9
Anthramycin/II	20 mg.	20	20/20	100	3-9
Anthramycin/II	30 mg.	10	10/10	100	3-10
Anthramycin/II	40 mg.	10	10/10	100	2-10
Anthramycin/II	50 mg.	10	10/10	100	3-10
Anthramycin/II	60 mg.	10	10/10	100	3-7
Anthramycin/2 (5886)	2.5 mg.	10	10/10	100	3-6
Anthramycin/2	5.0 mg.	10	10/10	100	3-10
Anthramycin/2	7.5 mg.	10	10/10	100	3-10
Saline	0.05 cc.	10	10/10	100	5-8
	1.5 cc.	10	10/10	100	6-9

earlier lots of anthramycin reduced the mortality slightly below that of the untreated control animals. The results of this study are summarized in Table I. It was noted that: the mortality of mice treated with M.B.T. = 0 per cent; the mortality of mice treated with anthramycin = 0-50 per cent and the mortality of untreated control mice = 50 per cent.

At 700 r of irradiation the M.B.T. effectiveness was still present, reducing the irradiation mortality to 8 per cent. The degrees of effectiveness of anthramycin against lethal irradiation appeared to depend upon the type, lot, and dosage injected. To ascertain similarities of effectiveness against lethal irradiation, the units of potency per milligram of fungal material

were coordinated whenever possible. (Potency indicated in units refers to a plate assay with *Torulopsis albida*.¹⁶) Upon regulation of dosages to a unit/mg. measure of potency, it was noted that 26 units of anthramycin/2 (C), a broth dialysate, gave a 30 per cent mortality and 30 units of anthramycin/15 (crystalline), an enriched solvent precipitate, gave a 25-30 per cent mortality as compared to an average mortality of 90 per cent when mice were treated with saline alone (Table II).

A 1,000 r treatment with M.B.T. or anthramycin prior to irradiation was not effective in curtailing mortality or prolonging survival time over that of the controls.

Subsequently, groups of mice with 2 cm. sarcoma 180 solid tumors propagated sub-

TABLE IV
MORTALITY AND SURVIVAL OF TUMOROUS MICE TREATED WITH M.B.T.
OR ANTHRAMYCIN 24 HOURS PRIOR TO IRRADIATION WITH 750 R

Bacterial or Fungal Product	Drug Dosage	No. of Mice Screened	30 Day Mortality	Per Cent Mortality	Mean Survival (days)
M.B.T.	0.05 cc.	20	18/20	90	12-30
Anthramycin/2 (5845)	7.5 mg.	10	4/10	40	25-30
Anthramycin/2 (5935)	0.05 mg.	10	7/10	70	11-27
Anthramycin/15	(30 units)	10	7/10	70	13-23
Saline	0.05 cc.	20	20/20	100	12

TABLE V

MORTALITY AND SURVIVAL OF TUMOROUS MICE TREATED WITH M.B.T.
OR ANTHRAMYCIN 24 HOURS PRIOR TO IRRADIATION WITH 1,000 R

Bacterial or Fungal Product	Drug Dosage	No. of Mice Screened	30 Day Mortality	Per Cent Mortality	Mean Survival (days)
M.B.T.	0.05 cc.	10	10/10	100	9-15
Anthramycin/2 (5886)	2.5 mg.	10	10/10	100	9-16
Anthramycin/2	5.0 mg.	10	10/10	100	4-13
Anthramycin/2	7.5 mg.	10	10/10	100	4-15
Saline	0.05 cc.	10	10/10	100	6-15

cutaneously in the supraclavicular area were studied. At 700 r there appeared to be an increase in survival time over that of the controls, although the decrease in mortality did not reach the level of that elicited in non-tumorous mice. At 1,000 r the tumor-

TABLE VI

CLINICAL EVALUATION OF ANTHRAMYCIN IN COMBINATION WITH
CONCURRENT THERAPEUTIC ROENTGEN IRRADIATION

Patient	Age	Sex	Histological Diagnosis	Duration of Treatment (days)	Drug Used	Route of Administration	Tumor Regression
J.R.	61	M	Squamous Carcinoma	43	Anthramycin B	I.V.	Yes
N.W.	59	M	Anaplastic Carcinoma	45	Anthramycin/2	I.V. and I.M.	Yes
N.N.	72	F	Infiltrating Anaplastic Adenocarcinoma	24	Anthramycin/2	I.V.	No
J.G.	74	M	Squamous Carcinoma	10	Anthramycin/15	I.V.	Unable to Evaluate
I.F.	62	F	Metastatic Anaplastic Carcinoma	52	Anthramycin C	I.M.	No
A.F.	41	F	Medullary Carcinoma				
			Infiltrating Anaplastic Carcinoma	29	Anthramycin/12	I.M., I.V., P.O.	Yes
			Medullary Carcinoma				
T.C.	76	M	Squamous Carcinoma	33	Anthramycin/2	I.V.	No
C.O.	50	M	Metastatic Anaplastic Carcinoma	42	Anthramycin B	I.V.	No
			Squamous Carcinoma				
G.C.	77	M	Anaplastic Carcinoma or Reticulum Cell Sarcoma	17	Anthramycin B	I.M.	No
R.B.	11	M	Hemangiopericytoma	66	Anthramycin/12 Anthramycin/15	P.O. I.V. and Nebulizer	Yes
A.B.	55	M	Metastatic Anaplastic Carcinoma	55	Anthramycin B	I.V. and I.M.	Unable to Evaluate
H.B.	56	F	Reticulum Cell Sarcoma	36	Anthramycin/15 Anthramycin/12	I.V. P.O.	Yes
S.B.	31	M	Epithelioma	11	Anthramycin/2	I.V. and I.M.	Unable to Evaluate
M.A.	54	M	Oat Cell Carcinoma	6	Anthramycin/12 Anthramycin/15	P.O. I.V.	Unable to Evaluate
H.A.	49	M	Squamous Carcinoma	39	Anthramycin/12	P.O.	Yes

I.V.=intravenous; I.M.=intramuscular; P.O.=oral route.

ous mice failed to respond to anthramycin or M.B.T. therapy; there was no increase in survival time.

DISCUSSION

Our survey of the protective effect elicited by anthramycin and M.B.T. against the lethal effects of irradiation indicates that M.B.T. provides the best protection to mice against lethal irradiation at 700 r. It became apparent that as dosage was increased the effect of mortality reduction and length of survival was decreased. The more purified anthramycin effectively reduced the mortality of the mice subjected to 600 and 700 r of irradiation, whereas the earlier lots of anthramycin reduced the mortality of the mice slightly below that of the untreated animals.

Studies in tumorous mice subjected to anthramycin or M.B.T. therapy prior to 700 and 1,000 r of irradiation did not demonstrate as good a protective effect. A dosage of 1,000 r was not effective in increasing survival time over that of the controls. Tumor regression should not be considered as a criterion of importance in the evaluation of the anthramycin antibiotic or M.B.T. as a protectant to these mice against irradiation. A lethal dose of irradiation was administered to the total body of each animal rather than as consecutive therapeutic doses given directly to the tumorous area itself. Mortality reduction did not reach the level elicited in the non-tumorous mice, while at 1,000 r response to anthramycin or M.B.T. therapy as a deterrent to death failed completely (Table III, IV and V).

CLINICAL EXPERIENCE

Fifteen patients with histologically proven cancer of various types have been treated with one or more fractions of anthramycin by the intramuscular, intravenous, or oral route in combination with roentgen irradiation. The results are summarized in Table VI.

DISCUSSION

The possibility of synergistic effects on

cancers by combining anthramycin or M.B.T. with roentgen-ray therapy cannot be evaluated fully as yet. Additional clinical investigation must be undertaken to confirm the preliminary clinical impression that the adjuvant therapy prevented some of the radiation toxicity while possibly increasing the cancericidal effect.⁹ The present study, however, indicates that neither anthramycin or M.B.T. interferes with the radiation therapy nor in any way potentiates the toxic effect of the irradiation.

SUMMARY

Our studies indicate that increased host resistance to irradiation is produced when M.B.T. or anthramycin is injected prior to exposure. The mechanism of protection with a therapeutic dose of M.B.T. or anthramycin is thought to be through stimulation of the hematopoietic and reticulo-endothelial systems—usually sites of severe irradiation injury. Lysosome studies have been conducted on microscopic sections of liver and spleen of mice treated with M.B.T. and anthramycin 24 hours prior to lethal irradiation of 700 r and, in contrast, of control mice treated with saline and like irradiation. Immediately following irradiation and on day 7, 14, and 21 post total body exposure, the organs were removed and the animals sacrificed. The tissues were fixed and stained according to the method of Barka and Anderson.⁶ Microscopic examination was made of the prepared slides to determine evidence of stimulation of the hematopoietic or reticuloendothelial systems through this medium. To date, insufficient evidence is available to clearly define the mode of action of these drugs. Additional clinical and experimental studies are needed to establish the active principle(s) the anthramycin and M.B.T. furnish for protection of a host against lethal irradiation and to evaluate the specific mode of action producing this effect.

Donald R. Cole, M.D.
Chemotherapy Unit
St. Vincent's Hospital and Medical Center
153 West 111th Street
New York, New York 10011

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MODIFICATION OF RADIATION RESPONSE OF TISSUE BY COLCHICINE* A CLINICAL EVALUATION

By MELVIN L. GRIEM, M.D.,† and FREDERICK D. MALKINSON, M.D., D.M.D.
CHICAGO, ILLINOIS

FREQUENTLY the radiotherapist is asked to deal with malignant tumors that are resistant to radiation at dose levels which can be tolerated by the surrounding normal tissues of the host. One approach might be to preferentially modify the radiosensitivity of the tumor or potentiate the effects of radiation within the tumor without producing a proportional increase in the radiosensitivity of the normal tissue.

Colchicine was considered as a radiation modifier for clinical evaluation. This drug has several interesting properties: (a) in mammals the highest concentration is found in the liver, gastrointestinal tract and in tumors;^{2,17} (b) the work of Taylor¹⁴ would suggest that the drug has an effect on spindle formation, thus affecting cells preparing for mitosis; and (c) Guyer and Claus⁸ and Brues, Marble, and Jackson³ suggested using it clinically together with irradiation with a 15 to 18 hour interval between drug and subsequent irradiation.

Our initial experiments were conducted on a microscopic hair indicator system to evaluate the extent of cellular damage of anagen hair matrix cells by colchicine and irradiation.⁷ Carworth Farms No. 1 female mice were plucked to induce the anagen phase of the hair cycle. This growing, or anagen phase, lasts from 17 to 20 days. Studies of the anagen phase of the proliferative cycle of the matrix cells suggest that these cells divide every 10 to 13 hours. On the tenth day after plucking, colchicine and roentgen rays were given in different sequences to study the degree of dysplasia or injury caused by these agents. Repeated

experiments suggested that pretreatment with colchicine 16 hours before irradiation induced maximum dysplasia. No protective effect of colchicine pretreatment was observed in the anagen hair experiments; however, Smith¹² reported the protective effect of colchicine when given 24 hours prior to total-body irradiation in rodents.

Following the hair experiments, we modified a method suggested by Friedman and Pearlman⁵ to evaluate several patients with mycosis fungoides. Single doses of roentgen radiation were administered at various time intervals after intravenous injection of colchicine. After 4 mg. of colchicine, the first patient showed maximum tumor response when colchicine preceded irradiation by 16 hours with no significant response at 4 and 8 hour intervals.⁷ The second patient is shown in Figure 1, which demonstrates the technique used and shows the variation in response associated with the different time intervals between prior injection of intravenous colchicine and administration of roentgen radiation.

With both animal and clinical evidence suggesting a 16 hour optimum interval between injection of intravenous colchicine and irradiation, a clinical trial was made on a number of patients with far advanced widespread malignancies who were considered inoperable and who were unsuited for palliative radiation therapy alone.⁶ In most patients, 4 to 5 mg. of colchicine was given intravenously, followed by a minimum radiation dose of 500 rads delivered to the tumor. This sequence was repeated every fourth or fifth day until a total tumor

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From the Departments of Radiology and Medicine (Section of Dermatology), The University of Chicago, and the Argonne Cancer Research Hospital (operated by the University of Chicago for the United States Atomic Energy Commission), Chicago, Illinois.
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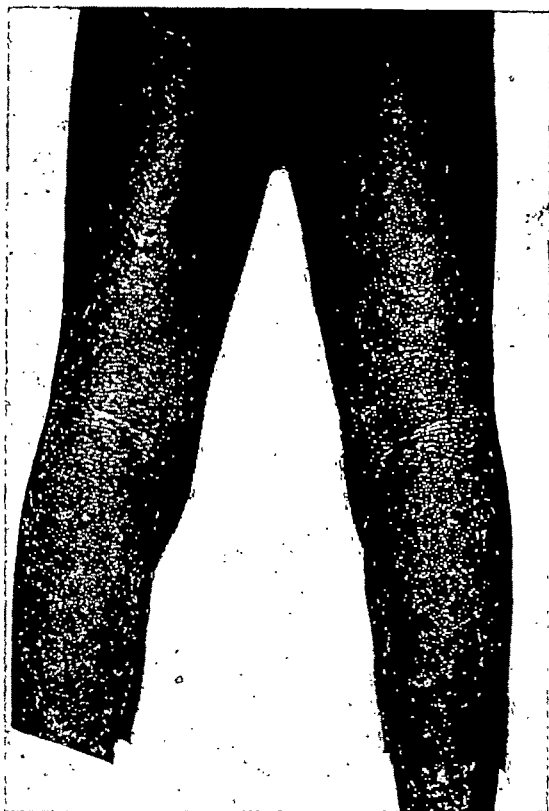


FIG. 1. A 30 year old white male with advanced mycosis fungoides in the infiltrative and tumor stage. Four milligrams of colchicine were given intravenously. Single exposures (150 kv., 50 F.S.D., 3 mm. Al filter) of 600 rads surface dose were administered to 7×7 cm. portals at 2, 4, 8, 12, 16 and 20 hours after injection. The 2 hour portal is just below the buttocks and the portals follow in sequence down the leg to the 20 hour portal just above the ankle.

dose of 4,000 rads was reached. In evaluating these cases, the following criteria were used:

(a) all lesions were histologically proven before treatment was started;

(b) all lesions were compared at autopsy or on the basis of histologic evidence; or

TABLE I
CENSUS

Total no. of cases	138
Autopsies	65
Dead, but no autopsy	61
Alive	12

(c) objective measurements of the lesions were made clinically or roentgenologically 2 to 6 months after therapy;

(d) where multiple lesions were available for study, a comparison of the effects of drug alone, irradiation alone or a combination of drug and irradiation was made. In such comparison studies the same sequence and fraction were used;

(e) where multiple lesions were not available, a total dose of radiation known to be well below the tumoricidal range was used for evaluation;

(f) subjective improvement was not considered.

Table I shows the number of cases in the study, the number of autopsies, the number of patients alive and the number of cases dead without autopsy. In the group in which autopsy was not obtained, a number of lesions were biopsied or removed surgically for histologic evaluation following treatment.

Table II shows the method of evaluation and the number of cases in each of the groups.

In Table III the histology of the type of lesion evaluated and the location of the lesion are given, together with the number of cases and the evaluation of the response in those cases. An impressive response was observed in patients with adenocarcinoma of the colon and adenocarcinoma of the stomach. In these 2 tumors the response was rather dramatic in the primary lesion; however, the treatment of the metastases

TABLE II
CRITERIA FOR EVALUATION AND
GRADING OF RESPONSE

Insufficient time for evaluation or lost to follow-up	23 (o)
No response to drug, irradiation or combined treatment	24 (—)
Response to irradiation without evidence of potentiation from colchicine	22 (*)
Patients showing objective response to combination of colchicine and irradiation	69 (**)

TABLE III
HISTOLOGIC EVALUATION

Type and Site of Lesion	No. of Cases		Grading of Response		
Adenocarcinoma of esophagus	4			2 (*)	2 (**)
Squamous cell carcinoma of esophagus	1		1 (—)		
Adenocarcinoma of stomach	22	3 (o)		4 (*)	15 (**)
Liver metastases treated	3	1 (o)		1 (*)	1 (**)
Adenocarcinoma of duodenum	1				1 (**)
Adenocarcinoma of colon	31	4 (o)	1 (—)	2 (*)	24 (**)
Liver metastases treated	4	2 (o)	1 (—)		1 (**)
Lung metastases treated	3		1 (—)	1 (*)	1 (**)
Bone metastases treated	2	1 (o)		1 (*)	
Skin metastases treated	1	1 (o)			
Adenocarcinoma of pancreas	11	5 (o)	1 (—)	3 (*)	2 (**)
Liver metastases treated	1		1 (—)		
Lung metastases treated	1	1 (o)			
Adenocarcinoma of gallbladder	2			1 (*)	1 (**)
Hepatocarcinoma	1		1 (—)		
Adenocarcinoma of lung	7		2 (—)	1 (*)	4 (**)
Undifferentiated carcinoma of lung	8	3 (o)	2 (—)	1 (*)	2 (**)
Squamous cell carcinoma of lung	5	1 (o)	2 (—)	1 (*)	1 (**)
Hypernephroma	5		5 (—)		
Melanoma	10		4 (—)	2 (*)	4 (**)
Mycosis fungoides	5		1 (—)		4 (**)
Adenocarcinoma of prostate	1	1 (o)			
Transitional cell carcinoma of bladder	2		1 (—)		1 (**)
Adenocarcinoma of thyroid	1				1 (**)
Adenocarcinoma of Gardner's duct	2			1 (*)	1 (**)
Undifferentiated carcinoma of ovary	1				1 (**)
Squamous cell carcinoma of skin	1				1 (**)
Neurogenic sarcoma	1				1 (**)
Adenocarcinoma of urachal origin	1			1 (*)	

of these tumors was somewhat disappointing. Several patients have gone over 3 years since the treatment of the primary lesions. At autopsy in 1 patient with adenocarcinoma of the stomach, only necrosis could be found in sites where the tumor existed previously. In several surgical and autopsy specimens, the only evidence of tumor was in the perineural area.

DISCUSSION

Bonomini and Fiorentino¹ have reported favorable clinical results combining colchicine and roentgen irradiation in the treatment of malignancies of the head and neck. Sutton¹⁸ has used colchicine and roentgen irradiation in the treatment of bronchogenic tumors with favorable results. The favorable results reported here in tumors

of the gastrointestinal tract could be explained on the basis of increased uptake of colchicine within these tumors.^{2,17} In this respect, the cyclic response to radiation following colchicine as observed in the patients with mycosis fungoides might have important implications; however, the cyclic response requires further investigation. It is possible that the 16 hour time interval between colchicine and irradiation is not the optimum time for all tumors.

Variations in radiosensitivity during the cell cycle have been observed by a number of investigators.^{9,11,15} Colchicine has long been known to arrest cells in metaphase.^{4,10} Some of the cells may escape this block, resulting in a synchronously dividing population. Van't Hof, Wilson and Colon¹⁶ have shown that colchicine can produce a par-

tially synchronous cell population through several cell cycles in pea seedlings. Such a synchronously dividing population may pass through periods of varying radiosensitivity.

Conceivably, the cells affected by colchicine are blocked in metaphase and subsequently die. This death may produce a stimulus for the remaining population to divide in a synchronous fashion, resulting in a cyclic response to irradiation. Using tritiated thymidine, further studies on the hair matrix cells using colchicine and irradiation are now in progress to increase our understanding of the population kinetics in a proliferative tissue.

SUMMARY

1. A clinical evaluation of the combined use of colchicine and irradiation is presented.

2. Adenocarcinoma of the gastrointestinal tract as well as mycosis fungoides showed favorable response.

3. A number of other tumors was surveyed.

Melvin L. Griem, M.D.
Department of Radiology
The University of Chicago
950 East 59th Street
Chicago, Illinois 60637

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INCREASED RADIOSENSITIVITY OF SKIN AND NORMAL TISSUES IN HIGH PRESSURE OXYGEN

By H. A. S. VAN DEN BRENK, M.S., F.R.C.S., D.T.R.
MELBOURNE, AUSTRALIA

A PRINCIPAL factor associated with the application of hyperbaric oxygen to radiotherapy is the possibility that normal tissues are sensitized to radiation damage and that their radiation tolerance is substantially reduced. Such sensitization has been particularly associated with relatively avascular normal tissues such as cartilage, presumed to be relatively anoxic. Thus Wright and Howard-Flanders²³ reported that the radiosensitivity of growing tail cartilages of mice breathing air was increased by exposing the animals to high pressure oxygen (HPO_2) at 3 atmospheres absolute (ATA), the oxygen effect factor in air being 2.34 and raised to 2.67 by HPO_2 . In clinical studies Churchill-Davidson *et al.*² considered that radiation damage to the normal laryngeal cartilage was increased in HPO_2 (3-4 ATA).

In better oxygenated vascular tissues such as skin, in animals and humans, HPO_2 would not be expected to produce further significant radiosensitization on the basis of the oxygen effect relationship given by the Alper-Howard-Flanders equation.¹ However, available experimental data and some clinical studies indicate that under ambient conditions of respiration in air, skin radiosensitivity is submaximal and increased quite substantially by exposure to HPO_2 or even to oxygen at 1 ATA. This paper reviews the relevant quantitative experimental data, clinical studies and also reports further experiments performed in rats, with a view to assessing the information these various studies provide in respect to the application of hyperbaric oxygenation to radiotherapy.

PREVIOUS EXPERIMENTAL DATA

Wilson²¹ scored acute skin reactions and depilation produced by x-radiation in legs

of anesthetized mice exposed to 10 per cent oxygen, air and 100 per cent oxygen, respectively. A quantitative method of scoring skin reactions was used. Wilson reported that 10 per cent oxygen reduced radiosensitivity by about 16 per cent while oxygen at 1 ATA increased radiosensitivity by about 10 per cent relative to air. Radiation reactions in legs of tumor bearing mice irradiated in air and in HPO_2 (4 ATA), respectively, were scored by a modified method by van den Brenk¹⁴ and a significant increase in skin damage resulting from HPO_2 was reported. These workers later performed further experiments with the same system using both single and fractionated x-ray doses and at various oxygen tensions.¹⁵ Sensitivity of skin in HPO_2 was increased, with DRFs (dose reduction factors) of 1.0 in anoxic conditions, produced by a tourniquet 1.7 in air and 2.7 in HPO_2 , respectively, *i.e.*, an increase of 60 per cent in HPO_2 relative to air. In these experiments it was shown that the radiation dose effect curves for anoxic and oxygenated (HPO_2) exposures were essentially parallel but that the slope of the air curve approximated towards the oxygenated value at lower doses (1,000 rads) but diverged towards the anoxic value at higher doses (4,000 rads). It was also shown that the radiation reactions in skin were diminished by fractionation of dose for all oxygen exposures investigated; also, if a tourniquet was applied to stop circulation in the leg, the mouse placed in HPO_2 and the skin below the tourniquet irradiated, its radiosensitivity was markedly increased by oxygen diffusing into the thin anoxic skin from without;¹⁶ indeed, the radiosensitivity was similar to that in air with an intact circulation. In a still further series of experiments¹⁶ giving fractionated doses of x-rays

under conditions of anoxia and air and HPO_2 breathing, respectively, the raised radiosensitivity of skin in HPO_2 was again demonstrated, and protraction of fractionation times was also shown to modify skin reactions, irrespective of oxygen effect. In clinical studies from the same laboratory⁶ Madigan reported that exposure of humans to oxygen at 4 ATA increased radiosensitivity of oral mucous membranes and, although similar increases were not so apparent in skin, the latter was difficult to assess in view of the quality of x-radiation (4 mev. x-rays) used. Subsequently, measurements of oxygen tension by a polarographic technique were made in both rat and human skin and tumors.^{3,4} In rat subcutaneous tissue, the p_{O_2} value recorded was 40 ± 2 mm. Hg if the anesthetized rat respired in air, while the corresponding p_{O_2} value increased 16 fold to 648 ± 117 mm. Hg when the rat was exposed to oxygen at 4 ATA. In human skin 65 per cent of air values were in the range 8–40 mm. Hg, and the corresponding mean HPO_2 (4 ATA) values for subcutaneous tissue were 320 mm. Hg. In human skin, only 15 per cent of electrodes registered less than 8 mm. Hg p_{O_2} and none less than 4 mm. Hg p_{O_2} —a finding which suggested that skin was at least sufficiently oxygenated for radiosensitivity to be at least 50 per cent in excess of anoxic values on the basis of the Alper-Howard-Flanders equation.¹ More detailed measurements of p_{O_2} in rat skin and calculations of oxygen effect factors indicate that radiosensitivity of skin in anesthetized rats was approximately 89 per cent of the maximum (fully oxygenated) value.

In humans, clinical studies of limbs irradiated under anoxia produced by arresting of circulation by a tourniquet have shown a great increase in radioresistance and a tolerance of radiation doses 2.5–3 times that in air with an intact circulation.^{18,10} Important studies by Suit⁹ in human volunteers exposed to small superficial x-ray fields, with and without the application of a tourniquet, gave an oxygen effect factor of approximately 2.5 for skin reactions.

Recently, similar studies using Sr^{90} applicators in anesthetized patients exposed to radiation exposures of 250–1,250 rads in high pressure oxygen at 4 ATA have been reported.²⁰ In each patient 8 fields were irradiated, 4 in air before exposure to HPO_2 and 4 after 15 minutes in HPO_2 at 4 ATA, with doses of 250, 500, 750 and 1,250 rads, respectively. Dose effect curves were obtained and gave an oxygen enhancement factor for HPO_2 (relative to air) which increased with magnitude of the dose from ~25 per cent at 250 rads to ~33 per cent for 1,250 rads doses, confirming experimental animal results.

In mice, a report by Withers and Scott²² confirmed the thesis that the radiosensitivity of skin in HPO_2 relative to air was increased, as reported by van den Brenk *et al.*¹⁶ and also that the difference was greater for higher doses. A series of further experiments reported here for thicker rat skin also confirms the various findings that skin radiosensitivity in HPO_2 is greater than in air, not only in respect to acute reactions but also in terms of delayed and residual radiation changes.

RADIOSENSITIVITY OF RAT SKIN AT RAISED OXYGEN TENSIONS METHODS

Male or female Albino Wistar Stock rats (170–250 gm. weight) were used. Before x-irradiation the animals were lightly anesthetized with pentobarbital sodium (nembutal), the hair over the dorsum and flanks removed with electric clippers, and a circular 2.0 cm. diameter area of skin exposed to single doses of superficial x-rays from a beryllium window source operated at 50 kv. (half value depth in tissue of 0.9 mm., dose rate in air 3.6 kilorads per minute) in the range 500–4,000 rads surface dose. The rats were irradiated within a special high pressure oxygen chamber described previously (van den Brenk *et al.*, 1962) which was modified by replacing the upper large thick irradiation portal by a steel plate with a radiation portal consisting of a 2 cm. in diameter thin (2 mm. thick-

ness) perspex insert. The rat was positioned in the vessel with the skin to be irradiated in contact with the under surface of the perspex portal. Doses were measured with a thimble ionization chamber placed in position in a phantom. For a 100 per cent dose measured at the skin surface, the dose was reduced to 65 per cent at 1 mm. below the surface. Previous experiments with different radiation qualities and filtrations giving half value depth doses in tissue in the range 1–4 mm. depth below the surface had shown that reactions produced were not significantly affected by variations in filtration and depth dose over this range. All radiations were given in the pressure vessel—whether the rat was irradiated in air at 1 ATA or exposed to HPO_2 at 4 ATA.

In each rat both flanks were irradiated, the one in air, the other in HPO_2 or test gas mixture. The rats were coded and randomized in respect to radiation doses and conditions of exposure, and skin reactions subsequently scored as “unknowns” by the one experienced observer. For exposures in HPO_2 , 15 minutes was allowed at pressure after flushing and compression at 1 ATA per minute, before irradiation, to allow tissue equilibration.

SCORING OF REACTIONS

The rats were examined twice weekly and skin reactions were classified according to a scoring method based on one reported previously¹¹ which is as follows:

Change	Index
No perceptible change	0
Mild erythema	1
Severe erythema	2
Dry desquamation	3
Moist desquamation	4
Skin loss (<33%)	5
Skin loss (33–66%)	6
Skin loss (>66%)	7

RESULTS

In Figure 1 a dose effect curve in air is shown for a series of experiments based on maximum reactions observed after irradiation

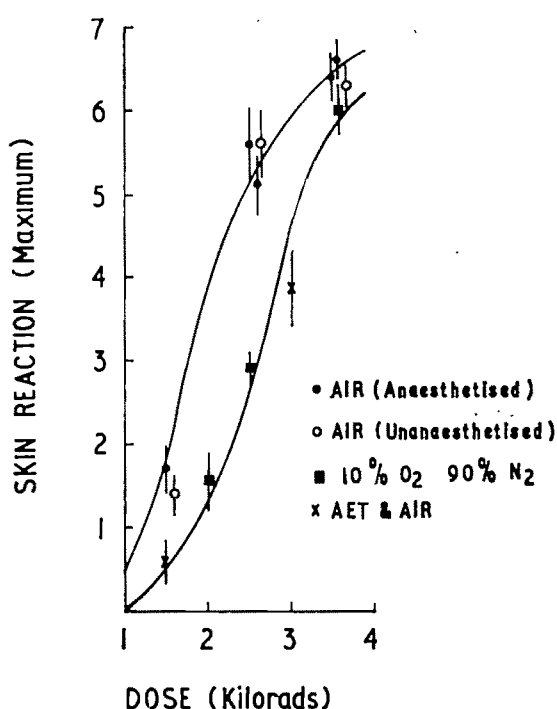


FIG. 1. Dose-effect curves for maximum reaction scored in rats irradiated with single doses when: (1) breathing air (anesthetized and unanesthetized); (2) breathing 10 per cent O_2 /90 per cent N_2 (unanesthetized); and (3) breathing air but pretreated with a single dose of AET, 15 minutes preceding irradiation under anesthesia.

tion in each irradiated skin, irrespective of time after radiation. The curve is sigmoid in shape with a maximum essentially linear rate of increase in the 2–5 unit reaction range corresponding to single doses of 1,500–3,500 rads. A dose (D_4) corresponding to a reaction level of 4 units and corresponding to a therapeutic “tolerance” level has been used to compare treatments. It is noted from Figure 1 that anesthesia did not significantly modify maximum skin reactions observed, while pretreatment of rats with AET (aminoethylthiuronium bromide HBr 300 mg. per kg.) caused a significant reduction in skin damage from a D_4 of 2,020 rads to ~2,950 rads for AET—an effect comparable to that achieved by pretreatment with other protective agents such as 5-hydroxytryptamine.¹² Exposure of rats to hypoxia (10 per cent O_2 /90 per cent N_2) during irradiation caused a similar reduc-

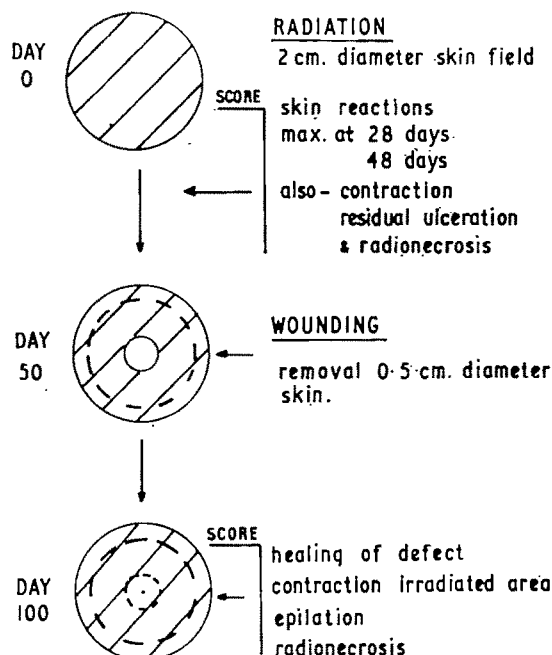


FIG. 2. Experimental design (see text).

tion in radiosensitivity of skin from a $D_4 = 2,020$ rads (air) to 2,850 rads (10 per cent O_2), an increase in dose tolerance of 141 per cent of the air dose—a value considerably

higher than that reported by Wilson²¹ but based on somewhat limited data for mice.

EFFECTS OF HIGH PRESSURE OXYGEN

In these experiments the scoring system used was the same as that above. Mean reaction levels were determined at 4 and 6 weeks post treatment, respectively, as well as the maximum reactions in each skin, irrespective of time. Since maximum reactions develop 2 to 3 weeks after exposure and subsequently abate, a progressive reduction in tissue reaction values with healing of desquamation and ulceration is followed by depilation and skin atrophy. To incorporate these residual changes a supplementary scoring system was used as follows:

Reaction	Score
Slight depilation (thinning of hair)	1
Moderate depilation	2
Complete depilation and significant atrophy	3
Complete depilation and severe atrophy	4
Residual ulceration (<33% irradiated area)	5
Residual ulceration (33–66% irradiated area)	6
Residual ulceration (>66% irradiated area)	7

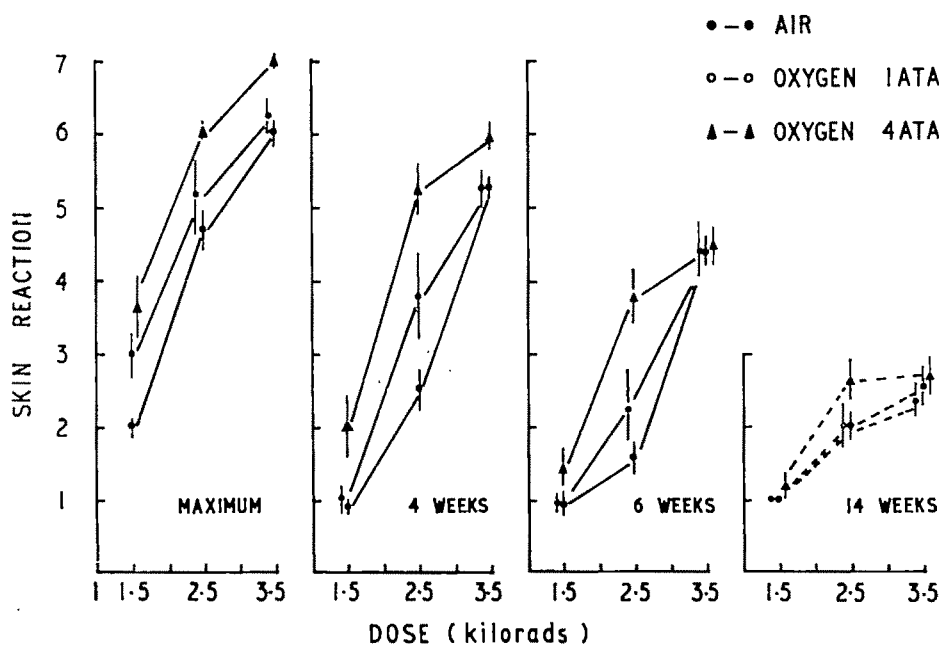


FIG. 3. Dose-effect curves for skin reaction and damage following x-radiation of skin of anesthetized rats in air, oxygen (1 ATA) and oxygen (4 ATA), respectively.

TABLE I

SKIN REACTIONS IN ANESTHETIZED ALBINO RATS IRRADIATED IN AIR OR OXYGEN AT 1 ATA OR 4 ATA RESPECTIVELY. SINGLE EXPOSURES OF 1,500-3,500 RADS X-RAYS (HALF VALUE DEPTH) = 2 MM. AL, 2.0 CM. DIAMETER CIRCULAR FIELD TO THE SKIN OF FLANK

	Dose		
	1,500 rads	2,500 rads	3,500 rads
<i>Maximum skin reaction irrespective of time</i>			
Air (1 ATA)	1.94 ± 0.06 (16)*	4.69 ± 0.26 (16)	6.00 ± 0.20 (16)
Oxygen (1 ATA)	3.00 ± 0.27 (8)	5.13 ± 0.55 (8)	6.25 ± 0.27 (8)
Oxygen (4 ATA)	3.63 ± 0.48 (8)	6.00 ± 0.00 (8)	7.00 ± 0.00 (8)
<i>Reactions scored 4 weeks post irradiation</i>			
Air (1 ATA)	0.88 ± 0.09	2.50 ± 0.30	5.25 ± 0.16
Oxygen (1 ATA)	1.00 ± 0.19	3.75 ± 0.60	5.25 ± 0.26
Oxygen (4 ATA)	2.00 ± 0.46	5.25 ± 0.37	5.88 ± 0.23
<i>Reactions scored 6 weeks post irradiation</i>			
Air (1 ATA)	0.88 ± 0.09	1.56 ± 0.21	4.44 ± 0.25
Oxygen (1 ATA)	0.88 ± 0.15	2.25 ± 0.50	4.38 ± 0.40
Oxygen (4 ATA)	1.50 ± 0.26	3.75 ± 0.37	4.50 ± 0.33

* Number of irradiated areas scored (mean ± SE).

DOSES (D_4) CORRESPONDING TO GIVE A REACTION OF 4 UNITS

	Oxygen (4 ATA)	Oxygen (1 ATA)	Air (1 ATA)
Maximum Reaction	1,650 rads (100%)	2,000 (121)	2,250 (136)
4 weeks	2,130 rads (100%)	2,700 (127)	3,070 (144)
6 weeks	2,900 rads (100%)	3,300 (114)	3,400 (117)
D_4 (Average)	2,166 rads (100%)	2,600 rads (121%)	2,883 rads (132%)

Also, to assess the "viability" and healing powers of irradiated skins, the experiment was designed as shown in Figure 2. Fifty days after irradiation, a 0.5 cm. circular area of skin was excised from the center of the irradiated zone by sharp dissection, to remove a full thickness of skin and the underlying *panniculus carnosus* muscle. Small residual nonhealed ulcers were often excised in this procedure, but where the ulceration involved a large portion of the irradiated zone, such irradiated flanks excluded from further analysis but classified as residual radionecrosis. No dressing was applied to the wounds after skin excision. At 100 days post irradiation (50 days post-wounding), the rats were examined and the following changes were recorded: (1) Healing of the wound (epithelization and con-

traction); (2) spreading radionecrosis, *i.e.*, death and ulceration of wound edges and adjacent irradiated skin; (3) condition of remaining irradiated skin in terms of epilation and atrophy (score 1-4 above); and (4) contraction of the entire irradiated zone (excluding those flanks with residual ulceration and epithelial defects), a reduction of the irradiated area to 50 per cent or less of the original field size being designated "marked contraction."

SKIN REACTIONS IN HPO_2 AT 1 AND 4 ATA

The results are shown in Figure 3 and Table 1, which also shows a calculation of D_4 values for maximum, 4 and 6 week values, respectively. In this experiment, two flanks were irradiated in each of 48 rats, the one in air, the other in 1 or 4 ATA

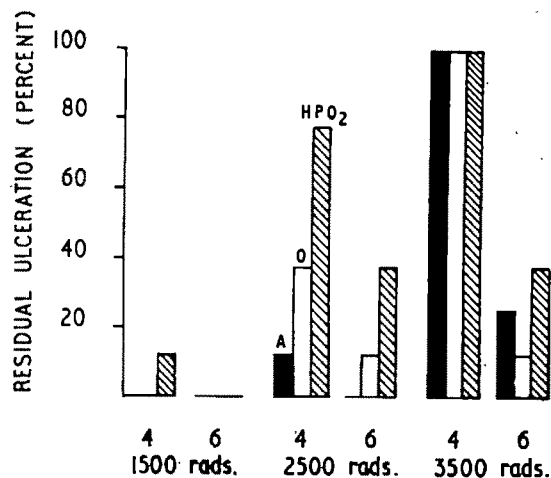


FIG. 4. Histogram of residual ulceration in irradiated skin scored at 4-6 weeks post irradiation in air and oxygen at 1 ATA and 4 ATA, respectively.

oxygen, and right or left flanks being randomized in respect to dosage and oxygen exposures. The results show that for every 100 rads in HPO₂ (4 ATA) an additional 21 rads were tolerated in oxygen at 1 ATA and an additional 32 rads in air. These results correspond closely to those obtained in human patients,²⁰ and clearly show radiation tolerance of skin to be reduced in HPO₂ with a DRF of 20-30 per cent for the dose range used. Furthermore, the DRFs obtained were similar for reactions scored at the maximum level of severity or during their subsequent resolution 4 to 6 weeks post irradiation.

Figure 4 shows the percentage of irradiated skins in which the irradiation resulted in epithelial loss (ulceration) which had failed to heal within 6 weeks post irradiation. An oxygen effect is clearly superimposed on the dose dependent incidence of epithelial loss. Figure 5 shows another example of relative skin reactions in air and HPO₂ for fractionated treatments.

DEPILATION IN HPO₂

Depilatory changes in these animals, 100 days after irradiation, are shown in Figure 3. While no difference could be detected for air and 1 ATA oxygen irradiations (D_2 value = 2,500 rads), for oxygen at

4 ATA the effect was more marked (D_2 = 2,100 rads), with an increased tolerance of an additional 20 rads per 100 rads for air and 1 ATA oxygen treatments. This result would suggest that in breathing air or oxygen at ambient pressure, a moiety of cells in the hair follicle progenitor cell system is radiobiologically anoxic.¹⁸ These cells appear less readily oxygenated than the corresponding skin basal layer, and hyperbaric oxygen pressures are required to effect their oxygenation and radiosensitization.

WOUND HEALING

The healing of the skin defect in the irradiated area was also dose dependent (Table II), but no significant enhancement by hyperbaric oxygen was detected. This



FIG. 5. Skin changes 6 weeks after irradiation in paired rats receiving fractionated x-irradiation (250 kv., half-value layer 1.5 mm. Cu) to right hemithorax. Dose $3 \times 1,000$ rads to surface skin on days 0, 7 and 14. Rat on left, treated in air, shows complete epilation. Rat on right shows residual skin necrosis and contraction of the entire irradiated skin.

result suggests that the over-all healing and repair process largely depends on regenerative and remodelling processes associated with the integrity of connective tissues of the base of the wound—tissues in which oxygen tension in respect to radiosensitivity is more optimal and which also received lower radiation doses—levels of radiation at which an oxygen effect becomes obscured and more difficult to reveal (Fig. 3), probably as a result of tissue and cellular recovery processes compensating for small differences in radiation damage. Also, wound healing in mobile rat skin is largely mediated by cell migration, remodelling and contraction,¹⁸ processes relatively resistant to radiation damage as distinct from cellular replication and proliferation. In the more "rigid" epithelial surfaces of humans, such contraction is relatively less efficient and cell replication plays a major role in the restitution of tissue defects by epithelial and repair tissues—conditions which would alter manifest radiosensitivity in humans and, perhaps, would be governed also by a great oxygen effect. Thus, unpublished studies by the author have indicated that wound contraction in rats is relatively insensitive to radiation and, furthermore, to be less dependent on the wound being irradiated in the oxygenated state than under conditions of anoxia or following the administration of radioprotective compounds.

CONTRACTION OF IRRADIATED ZONE

When a circumscribed intact area of mobile rat skin is irradiated, *the entire irradiated zone contracts if the dose given is sufficient to cause severe epithelial loss.* A

TABLE II

NONHEALING OF WOUND* (0.5 CM. FULL THICKNESS OF SKIN CENTER EXCISED FROM CENTER OF IRRADIATED SKIN 50 DAYS AFTER IRRADIATION. HEALING ASSESSED 100 DAYS AFTER IRRADIATION WITH SINGLE EXPOSURES OF X-RAYS)

Dose	Air (1 ATA)	Oxygen (1 ATA)	Oxygen (4 ATA)
1,500 rads.	1/13	0/6	0/6
2,500 rads	1/15	0/7	0/8
3,500 rads	3/14	2/7	1/7

* Includes radionecrosis of skin at 100 days.

Grade 3 reaction (dry desquamation) produces little contraction but a Grade 4 reaction (moist desquamation associated with patchy focal loss of epithelium) usually results in marked contraction (reduction of initial area by >50 per cent initial size) while reactions graded 5 or higher (ulceration) invariably produce marked contraction, even if the ulcerated area heals and epithelial continuity is restored. It follows, therefore, that the degree of contraction initiated in the surrounding unirradiated skin increases with doses in excess of 1,000–1,500 rads, and is an indirect index of radiation damage produced in the skin. In Table III the contraction is shown measured in irradiated skins at 100 days, excluding those treatments producing radionecrosis or nonhealed wounds. Contraction of irradiated skin is clearly dose dependent and its incidence also appears higher in oxygenated rats, particularly in the 4 ATA group at the 2,500 rads dose level. This result provides further evidence that epithelial skin damage produced by x-radiation is

TABLE III

IRRADIATED SKINS SHOWING MARKED CONTRACTION (>50% OF INITIAL AREA IRRADIATED) 100 DAYS AFTER IRRADIATION WITH SINGLE X-RAY EXPOSURES AND 50 DAYS AFTER WOUNDING* (SEE TABLE II)

Dose	Air (1 ATA)	Oxygen (1 ATA)	Oxygen (4 ATA)
1,500 rads	1/12 (8%)	0/6	1/6 (17%)
2,500 rads	0/14	1/7 (14%)	3/8 (37%)
3,500 rads	11/11 (100%)	5/5 (100%)	6/6 (100%)

* Excluding rats with radionecrosis or nonhealed wounds.

dose dependent and is enhanced by treatments given in HPO_2 .

DISCUSSION AND CONCLUSIONS

A review of published data, studied in conjunction with the further experimental results reported in this paper, clearly indicates that the radiosensitivity of intact skin of mice, rats and humans is substantially increased if the organism is exposed to raised oxygen tension during irradiation—particularly if hyperbaric (>1 ATA) pressures are used. Estimates of this high pressure oxygen enhancement factor, in terms of per cent increase in dose tolerated in air, give approximate values of 30–60 per cent increase in mice, 30 per cent in rats and 25–35 per cent in humans. It appears, therefore, that normal skin of these species under ambient air conditions contains a moiety of cells which are radiobiologically anoxic and radioresistant at any one time. This radioresistance is reversed if 100 per cent oxygen is administered during irradiation and is even more effective if the oxygen pressure is raised to 3–4 ATA. However, the magnitude of the radiation dose appears to influence the oxygen enhancement factor which appears to be less at lower doses, producing less severe reactions. This effect is probably an artefact inherent in the experimental system and due to a tissue recovery factor (reactive hyperplasia and cellular repopulation) which readily reverses the less profound damage to skin. Such recovery also modifies the shape of the dose-effect curve (Fig. 1) and probably accounts for the gradual increase in effect with increase in dose at lower doses.

Previous calculations of radiosensitivity of rat skin under euthermic, hypothermic and hyperthermic conditions²⁰ were based on measurements of skin p_{O_2} *in vivo*, and related to the Alper-Howard-Flanders oxygen effect equation:

$$\frac{S - S_n}{S_n} = (m - 1) \frac{[\text{O}_2]}{[\text{O}_2] + K},$$

where the constant $m = 3.1$ is taken as the limiting value for the oxygen effect factor,

and K is a constant expressing the value of the oxygen concentration $[\text{O}_2]$ in μM at which cell radiosensitivity (S) is raised to 50 per cent of the maximum value. Taking a value of $K = 10 \mu\text{M/l}$ the skin of euthermic rats (body temperature 32.5°C .) was calculated to be 89 per cent of maximum radiosensitivity, *i.e.*, equivalent to an increased tolerance of radiation dose of approximately 12 per cent. In these experiments for hypothermic rats (body temperature 15°C .), the calculated radiosensitivity of skin was decreased, corresponding to a further increase in dose tolerance of 3.4 per cent per degree Centigrade fall in body temperature to 15°C . A 5°C . fall in body temperature would correspond to the decrease in radiosensitivity of skin measured in air-breathing anesthetized rats. Thus the radiosensitization of skin by HPO_2 also appears supported by p_{O_2} values, particularly, if allowance is made for falls in skin temperature produced by anesthesia. Such hypothermia would tend to potentiate hypoxia in the skin of air-breathing rats and reduce p_{O_2} values (approximately 1 mm. Hg p_{O_2} per degree Centigrade fall in temperature) to levels of radiobiologic significance—a potentiation which would be completely obscured by the high levels of tissue p_{O_2} (>300 mm. Hg in skin) produced under hyperbaric conditions. This observation is of some importance in respect to the potential of hypothermia *in vivo* in reducing p_{O_2} and increasing tissue radiation tolerance. Attempts to protect the skin against radiation in air by local cooling⁸ are thus unlikely to be of similar effectiveness for irradiation in hyperbaric oxygen.

SKIN CIRCULATION IN HYPERBARIC OXYGEN AND ANESTHESIA

The barbiturate anesthetic used during treatment of humans by irradiation in hyperbaric oxygen in this Unit caused a fall in skin temperature of less than 1°C . per hour¹⁸ and would not produce significant anoxia in modifying radiosensitivity *per se*. However, the hypotension produced by the anesthetic could conceivably cause hypoxia

but this is reversed by pressurization of the patient in oxygen.²⁰ The lack of effect of anesthesia on radiation reactions in skin of rats (Fig. 1) suggests further that the anesthetic in itself is unlikely to produce hypoxia of sufficient magnitude to modify the radiosensitivity.

THERAPEUTIC RATIO FOR RADIATION TREATMENTS IN HYPERBARIC OXYGEN

Accepting the results that skin and, perhaps, other well vascularized tissues which are important in respect to dose tolerance in radiotherapeutics such as mucous membranes, are sensitized by HPO_2 by an oxygen effect factor of 2.3 (air) to 3.0 (high pressure oxygen at 4 ATA), it is important to relate this sensitization of normal tissues to the use of HPO_2 in radiotherapy of cancer. Crucial problems which arise in this respect are: (1) Clinical trials, the comparison of conventional air and HPO_2 irradiation and the doses used in such trials; (2) dose reduction in HPO_2 for comparable tumor cell sterilization and clinical effect on tumors; and (3) the magnitude of the therapeutic ratio of cancericidal effect in HPO_2 relative to air treatments allowing for increased normal tissue reactions in HPO_2 .

It becomes clear that any radiotherapeutic trial designed to evaluate the advantages of hyperbaric oxygen in clinical radiotherapy must not only exclude complications arising from modifications of fractionation and protraction of dose used in such treatments but must also be *based on the administration of doses producing equal normal tissue reactions and damage in air and HPO_2 , respectively, and these doses must be adjusted to comparable levels of tissue tolerance irrespective of their potential cancericidal actions based on theoretic deductions.*

Assuming that the parameters of both normal and neoplastic cell radiosensitivity are similar and that cell survival is based on the equation:

$$\frac{n}{n_0} = 1 - (1 - e^{-D/D_0})^m,$$

where D_0 (fully oxygenated) = 130 rads and the extrapolation value $m=4$, and if the maximum oxygen enhancement factor (in HPO_2) is approximately 3, certain comparisons may be made in respect to dose tolerance and therapeutic effectiveness of a dose of radiation based on the findings that a 20–30 per cent increase in dose is tolerated by normal tissues in air as opposed to HPO_2 . If a replicating system is fully oxygenated, 3×900 rads gives a surviving fraction (n/n_0) of approximately 10^{-8} . Let it be assumed that this degree of cellular lethality is required to produce a clinically acceptable incidence of tumor regression or cure in HPO_2 , and that this dose is tolerated by the normal tissues under the conditions of fractionation and protraction of dose (3×900 rads in 3–4 weeks) prescribed in HPO_2 . If the same irradiation dose was given in air, owing to partial anoxia of normal tissues, reactions would be less and the dose given could be increased to approximately $3 \times 900 \times 1.2$ or approximately $3 \times 1,100$ rads to result in similar tissue reactions. If the tumor under such ambient air conditions contained an anoxic cell element of 10^{-2} (a commonly quoted value for tumors), calculation shows that the dose of $3 \times 1,100$ rads in air would give a surviving tumor cell fraction (n/n_0) of approximately 10^{-8} . Thus, despite the increased tolerance of normal tissues in air, the sterilizing effect on the tumor irradiated by $3 \times 1,100$ rads in air is considerably less ($n/n_0 = 10^{-8}$) than that ($n/n_0 = 10^{-8}$) for a dose 3×900 rads in HPO_2 producing similar tissue damage. Indeed, the dose in air would need be increased to $\sim 3 \times 2,700$ rads (considerably in excess of tolerance levels) to produce a comparable cancericidal effect of $n/n_0 = 10^{-8}$.

It follows that if indeed clinical experience results in the conclusion that less difference exists for the effectiveness of radiation doses administered in air and HPO_2 , respectively, this can only be due to the presence of an anoxic tumor cell moiety of less than 1 per cent of tumor cells or some failure of the tumor to become oxygenated

TABLE IV

TOLERANCE DOSAGE IN HPO_2 AND AIR TO PRODUCE A BIOLOGICAL EFFECT — $(n/n_0) \approx 10^{-8}$ (FULLY OXYGENATED)

Protraction	1 Treatment per Week	1 Treatment per Week	2 Treatments per Week	3 Treatments per Week	5 Treatments per Week
Dose in HPO_2 *	3×900 rads	4×730 rads	6×542 rads	12×347 rads	20×260 rads
Dose in Air Corrected for Skin Sensitization Factor in HPO_2 (1.2) $(n/n_0)^\dagger$	$3 \times 1,100$ $(n/n_0 = 10^{-2})$	4×900 $(n/n_0 = 10^{-2})$	6×680 $(n/n_0 = 10^{-2})$	12×420 $(n/n_0 = 4 \times 10^{-3})$	20×310 $(n/n_0 = 10^{-2})$

* Calculated for $D_0 = 125$ rads, $m = 4$, assuming no repopulation between fractions.† Biologic effect for tumor based on an oxygen effect factor (F) of 3 (D_0 [anoxia] = 375 rads, m [anoxia] = 4) and the assumption that 1 per cent of tumor cells are radiobiologically anoxic.

in HPO_2 . It also follows from cell survival dose curves that the increased radiosensitivity of skin in HPO_2 , relative to air suggests that under ambient conditions possibly 1 in 10^4 – 10^5 skin cells is radiobiologically anoxic.

DOSE FRACTIONATION SCHEDULES IN CLINICAL EVALUATION OF HYPERBARIC OXYGEN

This is a predicament of considerable importance and little evidence is to be found in the literature that trials at present in progress or contemplated for the future are likely to provide conclusions which will not be challenged on the reasonable grounds that tissue tolerance may differ in the various conditions of treatment used in trials. Experience accumulated in the author's Unit and based on over 600 cases of advanced human malignancy treated in HPO_2 at 4 ATA with various doses and fractions suggests that a radiation dose given in HPO_2 , biologically equivalent to approximately $n/n_0 = 10^{-8}$, provides a substantial and therapeutically acceptable percentage of prolonged regression of advanced cancers, and if given as 3 to 6 fractions over 3 to 4 weeks, the dose is tolerated by normal tissues such as skin and mucous membranes according to generally accepted radiotherapeutic standards.

Recent clinical results with HPO_2 have shown that certain fractionated courses of radiation produce similar tissue reactions and rates of tumor regression. Thus, courses of $3 \times 1,000$ rads (0–21 days) and 6×600 rads (0–17 days) were similar in both respects, as were 3×800 rads (0–21 days) and

6×500 rads (0–17 days). Calculation of n/n_0 values for a $D_0 = 130$ rads shows that an extrapolation number of $m = 4$ provides a better fit than $m = 2$ for these clinical data for 3 to 6 fractions. It is suggested that in the calculation of biologically equivalent dose-fractionation schedules the value $m = 4$ should probably be used and, while a D_0 value of 125 rads (oxygenated) has been used in Table IV, this may be too low and a value somewhat higher (130–140 rads) should be chosen to express radiation reactions observed with different numbers of fractions, more accurately in terms of equivalent n/n_0 survival.

In Table IV a schedule of doses is suggested for 3 to 20 fractions administered over 3 to 4 weeks in air and HPO_2 , respectively, which should produce equivalent reactions and provide a basis for comparison of cancericidal effects in a clinical trial. It is suggested that a particular fractionation schedule should be chosen and that doses given in air should be ~ 20 per cent higher than HPO_2 doses to produce equivalent reactions in normal tissues. However, with larger numbers of smaller fractions, the experimental results suggest that the correction factor of 1.2 for air doses may be excessive²⁰ (Table I), although available data prevent a more definite estimate for fractionated treatments in this respect. Thus, the final decision would need to be based on progressive clinical observations made in a particular clinical trial. It is also necessary to emphasize that the HPO_2 sensitization factor is probably considerably less for certain tissues (e.g., intestinal mu-

cosa) since it was not possible to demonstrate a significant difference in LD₅₀ for whole body irradiation of rats in air and in oxygen at 4 ATA, respectively.¹⁷ Dose tolerance for pelvic and abdominal irradiation should therefore differ little for HPO₂ and air, respectively, and it would appear safer not to apply a dose tolerance correction factor. Irradiation of lung tissue of rats has also shown that this tissue is more radiosensitive in HPO₂ than in air⁷ and for thoracic irradiation the employment of a correction factor seems valid. Personal clinical impressions of tolerance of lungs irradiated in HPO₂ also suggest that this tissue may indeed be somewhat more sensitive in HPO₂.

These suggestions in respect to the evaluation of HPO₂ in clinical radiotherapy in no way attempt to estimate the advantages or disadvantages of fractionation or personal views regarding dose tolerance by a variety of tissues. The aim is simply to draw attention to the view that: (a) a comparison of relative cancericidal effects in HPO₂ and air, respectively, must be based on tissue reactions and damage which are similar for the two methods of treatment, and (b) certain normal tissues, including skin and mucous membranes, appear more sensitive in HPO₂ and by a dose reduction factor of approximately 20-30 per cent for doses within the range used in radical radiotherapy.

SUMMARY

1. Experimental and clinical studies are reviewed which provide evidence in respect to enhancement of radiosensitivity of normal tissues *in vivo* by exposure to hyperbaric oxygen.

2. The results of further studies of radiation reactions and damage in rat skin are presented which confirm previous observations that skin irradiated in air tolerates doses 20-30 per cent higher than doses administered in hyperbaric oxygen.

3. The application of these results to clinical studies and trials, designed to evaluate the use of hyperbaric oxygen in radio-

therapy of cancer, is considered. It is suggested that doses prescribed in air in such trials should be suitably corrected for this oxygen enhancing effect of hyperbaric oxygen exposures.

Radiobiological Research Unit
Cancer Institute Board
278 William Street
Melbourne, Australia

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EFFECT OF DAILY EXPOSURE TO HIGH PRESSURE OXYGEN ON TUMOR GROWTH*

By HERMAN D. SUIT, M.D., JANE SMITH, and CHIROTCHANA SUCHATO, M.D.
HOUSTON, TEXAS

ONE of the most promising developments in radiotherapy is the attempt to employ at a practical clinical level the potent radiation sensitizing compound, molecular oxygen, by having patients respire 100 per cent oxygen at 2-4 atmospheres of pressure (absolute) during local irradiation of the tumor.^{1,7} Recently, several institutions which are investigating the clinical efficacy of combining radiation therapy and high pressure oxygen (HPO₂) have adopted as their dose fractionation schedule: 30 equal radiation doses administered once daily, 5 days per week, for a total of ≈ 30 treatments in 6 weeks as contrasted with 2-6 treatments administered over 1-3 weeks in other and older clinical studies. The preliminary report from the Manitoba Cancer Foundation by Johnson⁸ is of special concern because their data raise the question: does daily exposure to high pressure oxygen for 6 weeks increase the growth rate of tumors? Twenty-five patients with Stage III and IV cancer of the uterine cervix were treated by 30 radiation treatments in a 6 week period and at each treatment they respired 100 per cent oxygen at 3 atmospheres pressure (30 psi, gauge). He prepared a "retrospectively matched series" or "control series" of 25 patients. At 6 months after treatment, 6 of the HPO₂ cases had developed widespread metastatic disease while only 1 in the "control" group had similar disease. The difference between the two groups is not significantly different, but does point out the need for careful observations of all patients who are in clinical trials of such combined treatment and of the need of relevant laboratory animal data. In this report the results of a study of

the effect of daily exposure to high pressure oxygen on the growth of a mammary carcinoma growing in laboratory mice are presented.

MATERIALS AND METHODS

EXPERIMENTAL ANIMALS

Young adult Strong A and BDF₁ [(C₅₇ × DBA)F₁] animals of both sexes were obtained from Texas Inbred Mouse Company, Houston, Texas. Adult Strong A and DBA animals bearing spontaneous mammary carcinomas were obtained from the same source. These animals were maintained at a constant temperature and humidity in the small-animal facility of this institution. Standard Purina pellets and water were supplied *ad libitum*. The animals were housed 8 per box.

TUMOR TRANSPLANTATION

Details of the tumor cell suspension preparation, viable cell counts, and tumor volume measurements have been given elsewhere.⁶ A volume of 5 to 10 μ l. of tumor cell suspension was injected either into the thigh muscle, subcutaneous tissue of the flank, peritoneal cavity, or into a tail vein. Transplantation into all animals (50 to 182) in any one experiment was performed from a single suspension of tumor cells. Three spontaneous tumors were used in these studies: one from a Strong A mouse and two from DBA mice. Transplants from one of the latter (exp. 45A) grew very slowly, *e.g.*, reaching a median volume of 239 mm.³ at 59 days after an injection of 2×10^5 viable cells intramuscularly (a 98 per cent transplant take rate). The tumor in the other two experiments grew much more

* From the Section of Experimental Radiotherapy, The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

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TABLE I
DETAILS OF EXPERIMENTAL PLAN

Experiment No.	Recipient Animals	No. of Animals Injected*	Site Injected	No. of Viable Cells Injected	Transplant Take Rate (per cent)
45A	BDF ₁	50	Thigh muscle	2×10^5	98
45C	BDF ₁	50	Thigh muscle	6×10^4	92
45D _A	Strong A	47	Thigh muscle	1.2×10^5	98
B	Strong A	53	Flank (subcutaneous)	1.2×10^5	98
C	Strong A	48	Intraperitoneal	2.5×10^5	98
D	Strong A	32	Tail vein	1.2×10^5	100

* These animals were divided into two groups of approximately equal size, a control and an experimental group.

rapidly, *i.e.*, reaching a median volume of 418 mm.³ and of 1,375 mm.³ 35 and 32 days after injection of 6×10^4 and 1.2×10^5 viable cells, respectively. However, for all three tumors there were grossly cystic and necrotic areas present in most of the tumor at the time of animal sacrifice. Tumors that developed in the control and the oxygen treated animals were similar in extent of cystic and necrotic areas.

HIGH PRESSURE OXYGEN (HPO₂)

A special lucite chamber (inside dimensions: 22.8 cm. diameter, 7.5 cm. high) was prepared for these studies.* The mice were placed inside a wire mesh cage with 16 compartments and this cage was put into the lucite chamber. For the experiments 45A and 45C, all animals (control and oxygen treated animals) were anesthetized by an

intraperitoneal injection of pentobarbital sodium, 0.07 mg./gm. body weight. No anesthesia was used in experiment 45D. The chamber was flushed for 1 minute by a flow of 10 l/min. of 100 per cent O₂; then pressure was increased at 12 psi/min. to a final level of 30 psi. This pressure and flow rate (10 l/min.) was maintained for 60 minutes and then depressurization effected at 30 psi/min. Oxygenation of the animals began either on the day of transplantation or the day following transplantation.

EXPERIMENTAL DESIGN

After transplantation, animals were assigned to the control or HPO₂ treatment group by use of a random number table. Details of the experimental plans are given in Table I.

END-POINTS OF STUDY

Data presented in this report were obtained from measurements on the day of

TABLE II
EFFECT OF DAILY EXPOSURE TO 100 PER CENT O₂ AT 30 PSI FOR 60 MINUTES FOR 6 WEEKS* ON GROWTH OF DBA MOUSE MAMMARY CARCINOMA TRANSPLANTED INTO THIGH MUSCLE OF BDF₁ [(C₅₇ × DBA)F₁] MICE

Experiment No.	Time of Tumor Volume Measurement	Median Volume of Tumor at Time of Animal Sacrifice†			
		Control‡		100% O ₂ at 30 psi	
45A	17 days after 30th oxygen treatment	239	(203 . . . 253)	152	(92 . . . 226)
45C	On day of 30th oxygen treatment	418	(268 . . . 503)	360	(150 . . . 544)

* Oxygen treatment given Monday through Friday, *i.e.*, a total of 30 exposures.

† Figures indicate 95 per cent confidence limits around median.

‡ Animals received nembutal anesthesia only.

TABLE III

EFFECT OF DAILY EXPOSURE TO 100 PER CENT O₂ AT 30 PSI FOR 60 MINUTES FOR 6 WEEKS ON GROWTH OF FIRST GENERATION ISOTRANSPLANTS OF STRONG A MAMMARY CARCINOMA (EXPERIMENT 45D)

Experimental Group	Transplant Site	Endpoint*	Control	100% O ₂ at 30 psi†
45DA	thigh	tumor volume (mm. ³)	1375 (870 . . . 1940)	1240 (930 . . . 1730)
DB	flank	tumor volume (mm. ³)	1200 (820 . . . 1330)	900 (770 . . . 1090)
DC	peritoneal cavity	tumor weight (gm.)	0.63 (0.30 . . . 1.04)	0.93 (0.65 . . . 1.85)
DD	intravenous	number of pulmonary nodules	20.5 (8 . . . 41)	21.5 (14 . . . 41)

* Animals in experimental groups A, B, and C were sacrificed immediately after the 27th, 28th, and 30th oxygen treatment, respectively. Animals in group D were sacrificed on the day following the 30th oxygen treatment.

† Oxygen treatment given Monday through Friday.

sacrifice of the animals; all animals in any one experimental group, control and study animals, were sacrificed on the same day. The time of sacrifice for each experimental group is given in Tables II and III. For thigh and flank tumor volumes, 3 diameters of tumors were measured and the volumes computed by the formula $V = 4/3\pi r_1 r_2 r_3$. Tumor nodules were counted in the following sites in all animals of experiment 45D: (1) peritoneal cavity (these were dissected from the animal and weighed); and (2) liver and lungs (the lungs were fixed for 24 hours in Bouin's solution before the nodules were counted). The medians of the samples were obtained, and distribution free confidence intervals were determined by reference to Table XVII of Lienert.⁵

RESULTS AND DISCUSSION

The results are listed in Tables II and III. The tumor volumes in the thigh and flank were the same for the control and HPO₂ groups within each of 4 experiments. In fact, the tumor volumes were slightly larger in the control animals, but this difference was not significant.

Similarly, as shown in Table III, neither the mass of tumor found in the peritoneal cavity nor the number of nodules in the lung tissue showed significant differences between control and oxygen groups. Although all data are not listed in Table III, no difference was noted between the control and oxygen treated animals in the number

of nodules in the peritoneal cavity, liver, or lungs following intraperitoneal or intravenous injection of cell suspension. In the animals with thigh and flank tumors, no metastatic lesions were found in periaortic lymph nodes, liver, or lung by gross examination of the specimens.

Of the 282 animals used in these experiments, there were 8 that showed no evidence of tumor at the time of termination of the study: 5 of these were in control and 3 in oxygen treated animals. The transplant take rate varied between 92 and 100 per cent for the various subgroups. Loss of animals during the experiment was 7 in the control and 14 in the oxygen treated animals. Several of these latter deaths occurred early in the experiment and were the result of pulmonary hemorrhage. Most of the other animal deaths occurred in the final week of the experiment 45D, and were due to the massive local tumor.

Kluft and Boerema⁴ reported that exposure of mice to 100 per cent oxygen at 3 atmospheres pressure for 2 hours, twice daily, for 11 days, retarded growth of a transplanted mammary carcinoma growing in subcutaneous tissue and in pulmonary tissue (after subcutaneous injection and intravenous injection of tumor cells, respectively). Hewitt² has found that the growth curve of a CBA mouse sarcoma following 2,300 r (in air) administered in a single treatment was the same in control or air breathing animals as in animals that re-

spired 100 per cent O_2 at 3 atmospheres of pressure for 60 minutes on day 0 to 13 after irradiation. These results are consistent with ours with reference to the point of interest of our experiment, *i.e.*, in neither study was there evidence of an enhanced growth of tumor in the oxygen treated animals.

SUMMARY

These results from studies of the growth of Strong A and DBA mouse mammary cancer in muscle, subcutaneous tissue, peritoneal cavity, and lung tissue did not indicate that tumor growth in these tissues was affected by exposure of the animal to 100 per cent O_2 at 30 psi for 60 minutes daily for 6 weeks during the active growth phase of the tumor.

Herman D. Suit, M.D.
Department of Radiology
Section of Experimental Radiotherapy
6723 Bertner Drive
Houston 25, Texas

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RELATION OF DOSE-FRACTIONATION OF X-RAYS AND ITS SPACING IN TIME TO SKIN DAMAGE*

EXPERIMENTAL STUDIES

By H. A. S. VAN DEN BRENK, M.S., F.R.C.S., F.C.R.A., D.T.R.
MELBOURNE, AUSTRALIA

FRACTIONATION of dose in radiotherapy is largely concerned with improving tissue tolerance. Much larger cumulative doses can be administered if the total dose is divided into fractions or increments and spread over a period of days or weeks. Quantitative studies employing experimental systems *in vitro* and *in vivo* have shown that increased tissue tolerance provided by fractionation is principally due to (a) the multihit characteristics of cellular damage and death produced by x-rays—based on the “Puck-Hewitt” cell survival curve;⁴⁻⁷ and (b) as a corollary to (a), rapid repair and recovery of “targets” in cells, sustaining partial radiation damage, is completed in less than 20 hours^{1,2} in respect to those targets associated with the capacity of a cell to divide, replicate and clone. However, other tissue recovery mechanisms play an important role in fractionation, particularly the capacity of uninjured cells to replicate and help to restore the cellular population of a tissue during a course of fractionated treatments. Such mechanisms depend not only on size of increments and their spacing in time but also on the regenerative capacities of a particular tissue.

Since these reactive capacities of tissues to repopulate are of vital importance to radiotherapy and therapeutic ratio of effect in cancer treatment, skin reactions due to radiation were studied quantitatively in rats to determine the effects of increment size and spacing of increments in time. The same cumulative dose of radiation was used to compare these effects of fractionation. Histologic studies were also made to aid in the interpretation of the results.

MATERIALS AND METHODS

Canberra black stock rats, weighing 200–250 gm. of either sex were used. The animals were lightly anesthetized with nembutal, and the hair was removed from the dorsal aspect of the trunk and flanks with electric clippers. In each rat 2 circular areas of skin, 2.0 cm. in diameter, were irradiated with a beryllium window x-ray source (150 kv., half-value depth 1 mm. tissue with zero added filter, dose rate 3,600 rad per minute). The applicator was covered by a thin stretched piece of melinex sheet to ensure flattening of the skin during irradiation. One flank received a single dose of 3,600 rads to the surface skin on day 0, the other the first increment of a fractionated course of radiation treatment totalling 3,600 rads cumulative dose. When fractionated treatments were subsequently delivered to this flank, the rat was re-anesthetized on each occasion. Right and left flanks in each group of rats were alternated for single and fractionated dose treatments. The fractionated treatments comprised $2 \times 1,800$ rads, $3 \times 1,200$ rads and 6×600 rads, respectively. These courses were given over periods of 2–28 days, but not less than 24 hours elapsed between any two successive exposures. Thus, in the 6×600 rad group, the shortest over-all time was 5 days for fractions given on days 0, 1, 2, 3, 4 and 5, respectively. In each time-fractionation group, 8 rats were used. In the 6×600 rads group, 1 rat in each of two groups died, probably from repeated anesthetics, before sufficient time elapsed after the first treatment to score reactions. All rats survived in the other groups.

The rats were coded and their skin reac-

* From the Radiobiological Research Unit, Cancer Institute, Melbourne, Australia.

tions were scored by a single observer twice weekly during the observation period, commencing 10 days after the first treatment. The acute reactions were scored on a quantitative basis as follows:

REACTION	SCORE
No observable change	0
Erythema	1
Marked erythema	2
Dry desquamation	3
Moist desquamation	4
Skin loss (<33% irradiated area)	5
Skin loss (33-66% irradiated area)	6
Skin loss (>66% irradiated area)	7

At 6 weeks after the last radiation treatment, an additional, modified scoring system was used to grade residual skin changes.

RESIDUAL REACTION	SCORE
No observable change	0
Graying but good growth of hair	1
Graying but thinning of hair	2
Patchy epilation	3
Complete epilation and atrophy	4
Skin loss and residual ulceration (<33%)	5
Skin loss and residual ulceration (33-66%)	6
Skin loss and residual ulceration (>66%)	7

For each group of 8 rats, the flank receiving a single 3,600 rad dose served as a control. The mean and standard error of the index of reaction was calculated for each treatment. The single dose treatment of 3,600 rads was chosen from past experience with this experimental system. It was known to cause, almost invariably, a grade 6-7 (near maximum) acute reaction within 2-3 weeks of irradiation.

To score acute reactions for each irradiated skin, the score chart was examined and the maximum recorded reaction, irrespective of time after irradiation, was defined as the *maximum acute reaction*. The *residual reaction* was scored at 6 weeks after the last radiation increment had been administered.

The rats were housed, 4 per cage, in an air conditioned animal room at $21 \pm 1^\circ \text{C}$. during the observation period.

For histologic studies, paraffin embedded sections were prepared and stained with hematoxylin and eosin. For mitotic counts animals were pretreated with colcemid 2 hours before sacrifice so as to accumulate C-mitoses in the basal layers of the skin. Mitoses per unit length of epithelium were scored but the appendages were ignored in counting the mitoses.

RESULTS

Dose Effect Relationship (single doses). Figure 1 shows the relationship between effect, expressed as the maximum acute skin reaction, plotted against single dose on a linear scale. Mean and standard errors are shown for a series of radiation doses from different experiments conducted over a period of years. The number of rat flank skins irradiated is shown against each point.

In our experience, results are very reproducible on a quantitative basis, despite the empirical allocation of "units" to grade the severity of acute changes—units which may or may not reflect more "fundamental" characteristics of radiation effects such as cell survival, replicative integrity, etc.

The dose (D_4), corresponding to moist

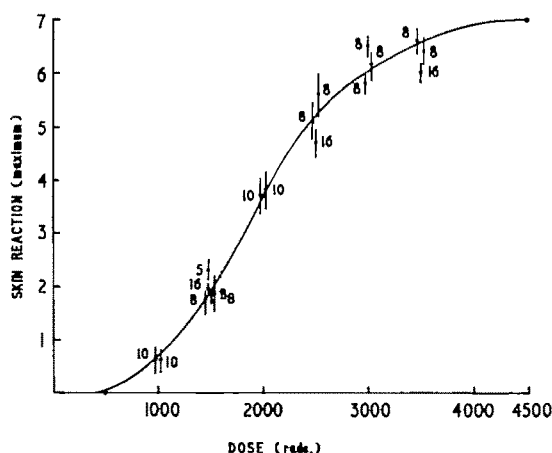


FIG. 1. Maximum reactions in rat skin plotted as a function of a single x-ray dose. Each point represents the mean and standard errors. The number of animals used is inserted at each point.

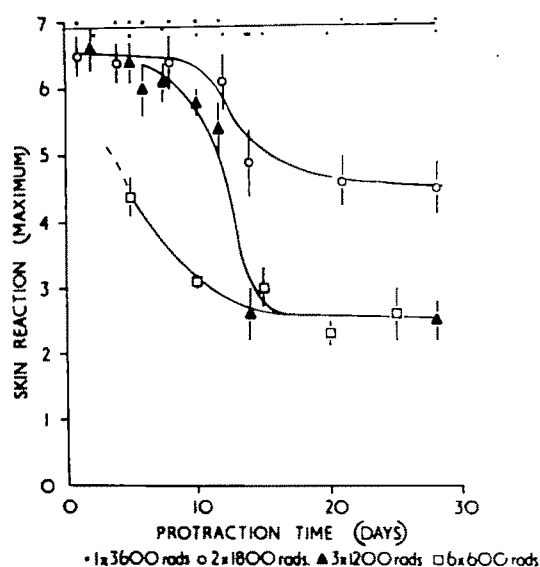


FIG. 2. Maximum reactions in rat skin plotted as a function of the over-all fractionation ("protraction") time for 3,600 rads divided into 2, 3 and 6 fractions, respectively, but spaced at different intervals. The reactions for control flanks receiving $1 \times 3,600$ rads on day 0, corresponding to each fractionated treatment, are plotted on the same time scale. Each point represents the mean and standard error for 8 irradiated skins.

desquamation, is a convenient level to compare modification of treatments (by fractionation, etc.) and is also of interest to clinical studies in that it is an expression of the maximum tolerated local reactions usually accepted by radiotherapists in respect to epithelial surfaces (skin and mucous membranes).

Time—Fractionation. These results are summarized in Figures 2 and 3 and show that the reactions and damage produced in skin by a fractionated course of x-radiation are profoundly dependent on increment size and spacing or "protraction" of the increments. The effect of protraction was also dependent on the size of the fractions.

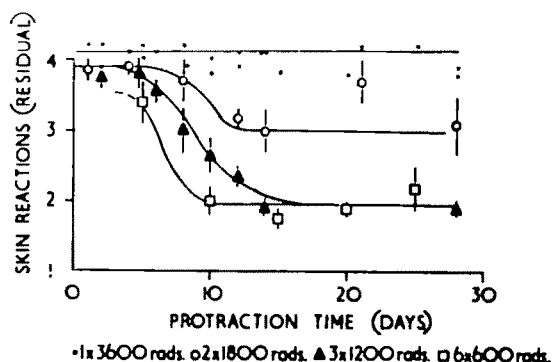


FIG. 3. As in Figure 2 but for "residual" reactions scored 6 weeks after the single or last fractionated treatments, respectively.

However, the general shape of the reaction—protraction curves for the cumulative dose given, was similar for increments varying in size and number. The relationships for maximum reactions were also similar to that of residual reactions and damage scored 6 weeks after the last radiation exposure. Conclusions drawn from the data presented in Figures 1 and 2 are as follows:

(a) For 2, 3 and 6 fractions used to administer a cumulative dose (D_c), protraction (T) beyond 14 days failed to significantly decrease reactions and skin damage.

(b) For protraction time $T > 14$ days, 2 fractions produced much less skin damage than a single dose. There was no significant difference between $3 \times 1,200$ rads and 6×600 rads, respectively, if the treatments were protracted beyond 14 days.

(c) For protraction time $T < 14$ days, all fractionated treatments produced progressively less reaction and damage as T increased from 0–14 days. The magnitude of this decrease with T was dependent on size of dose increments (D_f) and their number. This decrease in rats was most marked with the smaller increments. The most rapid decrease in reactions occurred for values of T in the following ranges:

D_c	Fractionation	T (protraction)	
		Acute	Residual
3,600 rads	($2 \times 1,800$ rads)	12–14 days	8–12 days
3,600 rads	($3 \times 1,200$ rads)	8–14 days	8–12 days
3,600 rads	(6×600 rads)	5–10 days	5–10 days

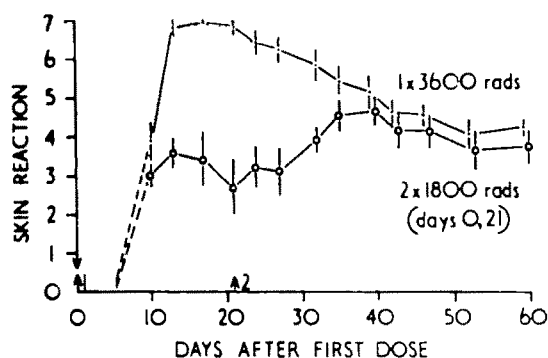


FIG. 4. Time course of development and resolution of acute skin reactions in a group of 8 rats which received $1 \times 3,600$ rads (day 0) and $2 \times 1,800$ rads (days 0, 21) to alternate flanks, respectively.

Figures 4, 5 and 6 show the development of skin reactions with time in rat flanks receiving single doses (3,600 rads) and contralateral flanks receiving fractionated doses, respectively. It is to be noted that fractionated treatments produced reactions which tended to be maintained at a steady but lower level than reactions corresponding to single doses in the contralateral flanks. For $2 \times 1,800$ rad treatments spaced at large intervals, reactions increase after each increment but never reach the maximum values corresponding to single doses. However, owing to prolongation of the reactions by the fractionated treatments (Fig. 6), these tend to approximate the subsiding reaction produced by the single dose technique. Thus, to assess "residual" damage (Fig. 3), an equal interval was allowed to elapse after the last treatment.

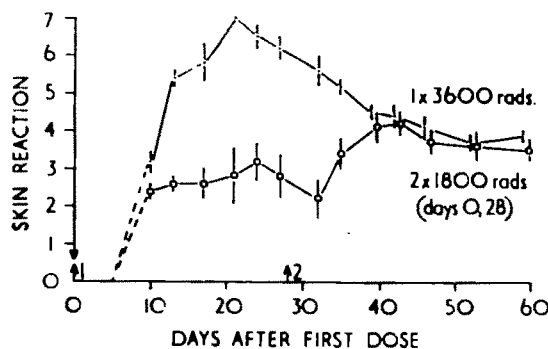


FIG. 5. As in Figure 4 but $2 \times 1,800$ rads administered on days 0 and 28.

A comparison of the fractionation results with the single dose technique (Fig. 1) shows that 2 fractions ($2 \times 1,800$ rads) protracted beyond 14 days produce an effect equivalent to approximately 2,200 rads using the single dose technique, while $3 \times 1,200$ rads and 6×600 rads, respectively, if similarly protracted over $T > 14$ days, cause an effect equivalent to that of a single dose of approximately 1,800 rads.

From the data provided by Figures 1 to 3, it is possible to estimate the single iso-effect doses (D_1) corresponding to a cumulative dose (D_N) given as N fractions, but with variation of the different over-all fractionation times (T). Such estimates for $T = 5, 10$ and 15 days, respectively, are shown in Table 1. Values of D_1 have also been expressed in terms of a cell surviving fraction (n/n_0) assuming a $D_0 = 130$ rads and an extrapolation number $m = 2$ and the "quasi threshold dose D_q "³ based on $D_q = D_N - D_1/N - 1$ has also been estimated. The present data show that the reduction of tissue damage produced by fractionation is highly dependent on fractionation time intervals, quite apart from the size and number of increments administered and that these various factors are interrelated. Thus, shorter courses of treatment (lower T values) and smaller fractions (600 rads) both tend to reduce D_q values while with larger fractions (1,200–1,800 rads) high D_q values (corresponding to enhanced tissue recovery) only result

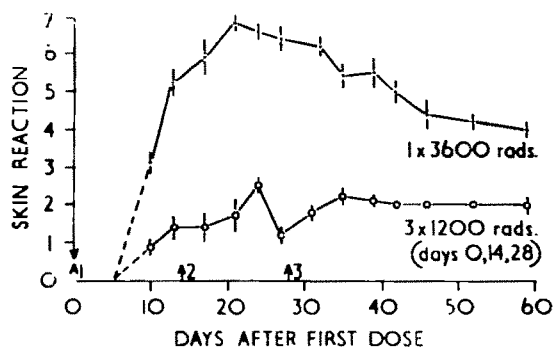


FIG. 6. As in Figures 4 and 5 but the fractionated treatment ($3 \times 1,200$ rads) administered on days 0, 14 and 28.

TABLE I

ESTIMATED VALUES OF CELL SURVIVAL AND QUASI THRESHOLD DOSE FOR SKIN REACTIONS PRODUCED ON RATS BY A CUMULATIVE DOSE (D_N) OF 3,600 RADS ADMINISTERED AS A NUMBER OF EQUAL FRACTIONS ($N=2, 3$ AND 6 , RESPECTIVELY) FOR DIFFERENT OVER-ALL PROTRACTION TIMES (T)

	Fractionation ($N \times D$)		
	2 $\times$ 1,800 rads	3 $\times$ 1,200 rads	6 $\times$ 600 rads
$T = 5$ days			
Single Iso-Effect Dose* (D_1)	3,500 rads	3,400 rads	2,200 rads
n/n_0 (Calculated for D_1)†	4.1×10^{-12}	8.8×10^{-12}	8.9×10^{-8}
Quasi Threshold Dose " D_Q "‡	100 rads	100 rads	280 rads
$T = 10$ days			
D_1	3,300	2,800	1,850
n/n_0	1.9×10^{-11}	8.8×10^{-10}	1.3×10^{-6}
" D_Q "	300 rads	400 rads	350 rads
$T = 15$ days			
D_1	2,350	2,000	1,700
n/n_0	2.8×10^{-8}	4.2×10^{-7}	4.2×10^{-6}
" D_Q "	1,250 rads	800 rads	380 rads

* Based on data in Figures 1 to 3.

† Calculated from $n/n_0 = 1 - (1 - e^{-D/D_0})^m$ for $D_0 = 130$ rads, $m = 2$.

‡ " D_Q " = $(D_N - D_1)/(N - 1)$ after Fowler (1965).

when T is increased beyond 10 days. Thus, any attempts to formulate equivalent dose-effect relationships for larger fractions (particularly in excess of 600 rads) are quite erroneous if the effect of variation in time interval between fractions is ignored. Indeed, such an omission could have disastrous consequences in radiotherapeutics—not only with roentgen rays but with high LET qualities in which the shoulder of the cell survival curve is reduced with corresponding reductions in the "Elkind effect."

Histologic Changes in Mouse Skin (Fig. 7, A-D). The dorsal skin of a hairless mouse strain was chosen. When a section of unirradiated dorsal skin in this species (Fig. 7A) is compared with skin 14 days after irradiation with a single dose of 1,500 rads (Fig. 7B), it is clear that the epidermis has undergone a *marked compensatory hyperplasia* with a 3 or 4 fold increase in thickness and abundant mitoses in the basal layer. Similar skin, 14 days after a single dose of 3,000 rads (Fig. 7C), shows almost complete loss of epidermis and ulceration

and no significant epithelial cell repopulation except at the margins of the irradiated zone (Fig. 7D), where the dose delivered is reduced due to the penumbra effect and only a marginal hyperplastic reaction similar to that for 1,500 rads (Fig. 7B) occurs. Thus, cellular damage from increments of 1,000–2,000 rads results in a reactive hyperplasia which facilitates tissue repopulation and "over-compensates" for the damage produced by the treatment. Furthermore, if ample time elapses to allow a sufficiently large population of cells to accumulate, this offsets damage due to a further radiation increment. However, with large dose increments, cell loss may be so marked that only scattered islets of hyperplastic epithelium remain. Such islets may fail to survive in the ulcerated milieu and degenerate, thus failing to act as efficient regenerative zones which can result in healing. An example of such degeneration of hyperplastic epithelium in rat skin is shown in Figure 8, 28 days after a single dose of 2,500 rads.

Mitotic Counts. Figure 9 shows mitotic

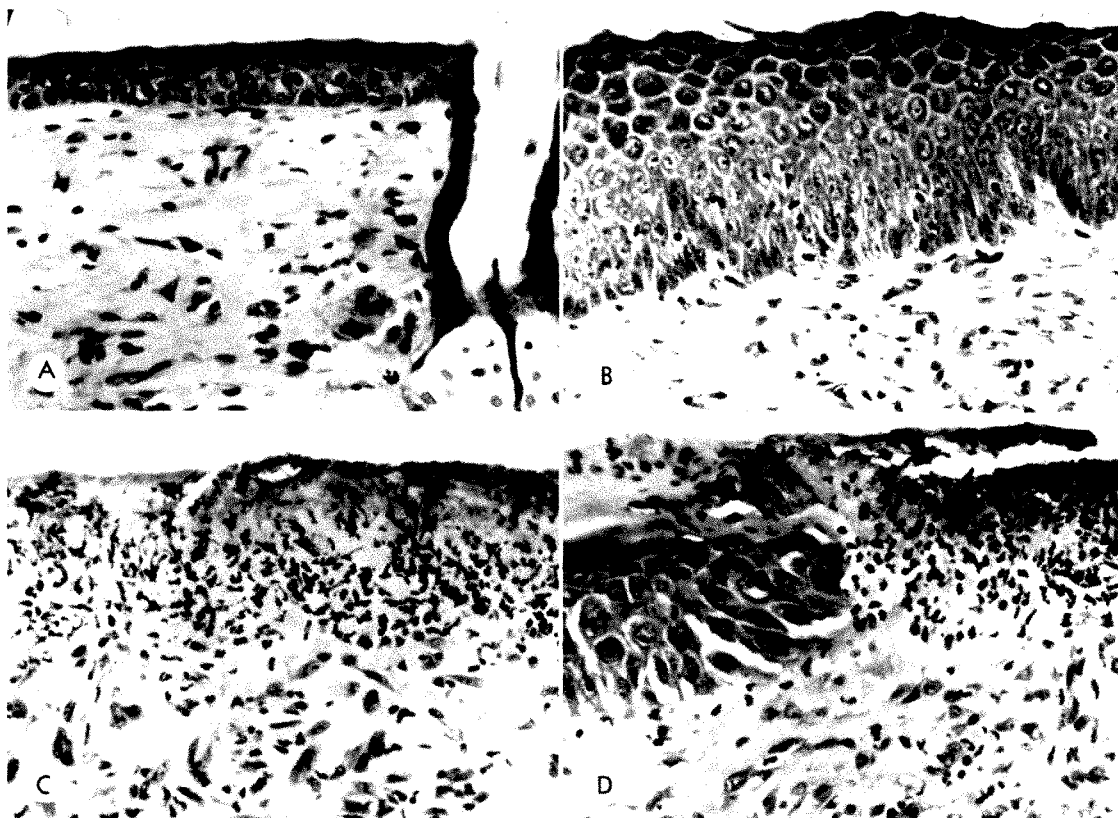


FIG. 7. (A-D) Histologic sections of skin of hairless mice (H&E $\times 500$). (A) Normal unirradiated skin (atrophic hair follicle also shown). (B) Fourteen days after single fraction of 1,500 rads showing marked hyperplasia and repopulation of epidermis with numerous mitoses in basal layers. (C) Fourteen days after 3,000 rads showing almost complete necrosis of epidermis. (D) Edge of field in C (14 days after 3,000 rads) and hyperplastic reaction in epidermis on left of photograph where dose "fall-off" occurs, with necrosis on right where full dose of 3,000 rads was received by the epidermis.

counts made in irradiated skin of rats injected 2 hours before sacrifice with colcemid to accumulate C-metaphases.

The largest dose (2,500 rads) used produced progressive mitotic depression which failed to replace the dying epithelium over the first 14 days. An intermediate dose (1,500 rads), permitting the survival of sufficient cells capable of replication in the basal layers, produced a delayed reactive hyperplasia with very high mitotic counts at 10-14 days. The low dose (500 rads) used produced an earlier cellular recovery and compensatory hyperplasia (at <10 days) but mitotic rates were lower than after larger doses.

These histologic studies clearly show that hyperplastic reactions play an essential role in the recovery of tissues from radiation

injury. Such hyperplastic changes are seen in all other forms of cellular injury and depopulation. If the mathematics of cell survival data are applied to tissue recovery and restoration following radiation exposure, the dynamics of cellular repopulation must be taken into account and not oversimplified. The "quasi threshold dose D_q " concept is considered a particularly oversimplified parameter in respect to tissue tolerance *in vivo*.

DISCUSSION

The radiotherapeutic and radiobiologic literature in recent years abounds with commendable but somewhat premature attempts to calculate tissue tolerance to roentgen rays and tumor effects *in vivo* in terms of cell survival provided by highly

sophisticated experimental methods, such as those of Puck and Marcus,^{6,7} Elkind and Sutton,^{1,2} Hewitt and Wilson,^{4,5} and Till and McCulloch⁹—methods in which cell survival can be much more accurately defined and calculated than in the complicated milieu of intact tissues and organs of mammals *in vivo*.

The aim to quantitatively predict effects of fractionation of dose *in vivo* in terms of cell survival, radiation dose parameters (D_0 , " D_Q " and extrapolation values) may

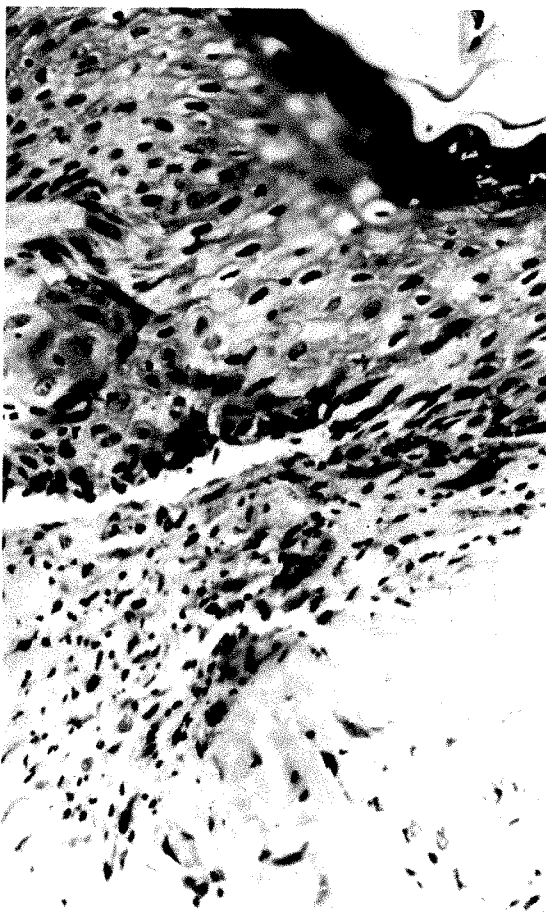


FIG. 8. Section of rat skin, 28 days after single exposure of 2,500 rads, showing degeneration and "lifting" of a hyperplastic islet of regenerated epidermis, with fraying of the basal layers into the underlying stroma and undergoing pyknosis and degeneration. The more mature surface layers of epidermis appear largely intact but subsequently degenerate. This results in complete ulceration which fails to heal in the absence of a basal cell population capable of division, replication and regeneration of all epidermal layers.

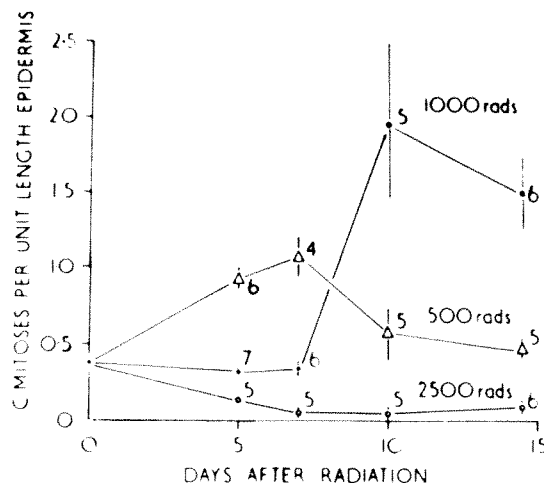


FIG. 9. Mitotic counts in rat epidermis with time after single doses of 500, 1,000 and 2,500 rads, respectively. Each point represents the means ($\pm$ SE) calculated for 40-60 pooled serial microscopic fields in each of 4-6 rat skins (animals pretreated with colchicine before sacrifice—see text).

be fundamentally sound, but the complexities of tissue recovery and reactive mechanisms should not be oversimplified. Previous attempts to formulate iso-effect doses for fractionated treatments such as those by Strandqvist,⁸ while largely empirical, were based on fitting a set of clinical data by the best available quantitative dose-effect relationship. Indeed, Strandqvist's linear log D_N —log T relationship was established from careful clinical observations and has proved an acceptable basis for dose-equivalence in radiotherapeutics since its formulation—provided it is not extrapolated beyond the conditions of treatment originally defined by Strandqvist, *i.e.*, daily fractions to a maximum of 40-50 treatments, given to relatively small areas of the integument. Strandqvist's analysis was largely based on the conventional radiotherapeutic policy of administering daily fractions, and the data did not allow for its extrapolation for single doses or a few large fractions. Indeed, an analysis of the incidence of late radiation necrosis following therapy of skin cancer with a few (4-5) large fractions compared with several (9-18) smaller fractions was made by Traenkle

and Dattatreya.¹⁰ These authors clearly showed a higher (14 per cent) incidence of late necrosis with the large fraction regimen compared to 3 per cent for the small fraction group. They showed that this result was not in accord with Strandqvist's curve but was related at least partly to differences in over-all fractionation time, comparable tissue recovery after a large fraction being more delayed.

The present data for rat skin show that:

(a) For single doses, the shape of the dose effect curve (Fig. 1) is complex and skin reactions, arbitrarily graded, are not directly proportional to cell surviving fractions, although the latter may well be the primary underlying factor.

(b) For 2-6 equal large fractions, the acute and delayed effects produced in skin are highly dependent on their spacing (protraction) in time in the range of approximately 0-14 days. Beyond 14 days further delays between treatments produced little further increase in tolerance. This maximum period of 14 days post irradiation appears to correspond to the delay in onset of *effective* reactive hyperplasia after a large dose increment. While larger doses (> 2,000 rads) may be compatible with the production of hyperplasia, the over-all damage is usually one of total epithelial loss over wide areas. This cannot be effectively repaired by scattered focal reactions originating in surviving small numbers of skin cells, and tissue tolerance is exceeded (radionecrosis). Thus, as shown in Figure 2, a reaction in excess of moist desquamation (4 units), corresponding to a single dose of approximately 2,200 rads or its fractionated equivalent, is borderline in exceeding tissue tolerance by producing "acute radionecrosis," defined as a sufficient breach of epithelial continuity to result in macroscopic ulceration.

It is interesting to note that this single dose of 2,200 rads, which sets an upper limit to tissue tolerance in rat skin, also corresponds closely to the maximum single dose generally considered to be tolerated by human skin. Figure 2 also shows that the

fractionated dose producing moist desquamation (D_4) in rat skin is given by:

$$1 \times 2,075 \text{ rads}$$

$$3 \times 1,200 \text{ rads in 13 days } (D_Q = 762 \text{ rads})$$

$$6 \times 600 \text{ rads in 6 days } (D_Q = 305 \text{ rads}),$$

while $2 \times 1,800$ rads exceeds tolerance irrespective of over-all fractionation time. Thus, these values for " D_Q " and those shown in Table 1 indicate that, for fewer but larger fractions, the value of D_Q largely depends on time intervals between fractions, a dependence not adequately stressed in the calculations of Fowler³ in an attempt to formulate biologically equivalent radiotherapeutic doses in terms of tissue tolerance for fractions (differing in magnitude and number) administered, irrespective of over-all fractionation time. Indeed, the experimental data available suggest that the "high values" of D_Q obtained for skin reactions in mouse, man, pig and rat are largely due to tissue recovery factors and mechanisms, which compensate for perturbation in cell population dynamics produced by irradiation. Such mechanisms depend on spacing of fractions adequate to allow efficient cellular repopulation to occur. The present experimental results, supported by the human data of Traenkle and Dattatreya,¹⁰ and others, suggest that the magnitude of cell repopulation in tissues is particularly important if large radiation fractions are given. As previously reported from this laboratory,¹¹ clinical experience in the use of large fractions in humans irradiated in high pressure oxygen has led to similar conclusions. Thus, in irradiation of the pelvis, acute lethal bowel damage commonly results if the small intestine receives $3 \times 1,000$ rads megavoltage at weekly intervals. If the treatment intervals are extended to 14 days, morbidity is greatly reduced for dose increments of equal magnitude and number.

SUMMARY

Prolongation of fractionation times greatly modifies the intensity of the reac-

tions, irrespective of the number and size of fractions delivered. This is due to a perturbation of cell population dynamics and the time factors involved in the onset of reactive hyperplasia. The results indicate that iso-effect dose formulae for fractionated treatments in radiotherapy, based on experimental animal and cell survival data, are of doubtful validity if dose-time factors which modify repopulation dynamics are ignored. This particularly applies to treatments in which a limited number of large fractions are used. For large dose increments in the range 1,200–1,800 rads, spacings in excess of 14 days between successive fractions do not improve tissue tolerance but tissue tolerance decreases progressively as the interval is reduced to approximately 6 days, below which a further decrease has little effect in modifying damage. Doses of 600 rads produced similar effects but prolongation of such treatments with spacings between fractions in excess of 3 days did not improve tissue tolerance further.

In the various tissues of different species, the results of fractionation in respect to time will differ according to cell turnover rates, the capacity of tissues to regenerate and undergo hyperplasia in reaction to damage. These factors invalidate an oversimplification of tissue tolerance and effects in terms of any single "iso-effect-dose" formula designed to provide the radiotherapist with a "ready-reckoner" for calculation of doses.

Radiobiological Research Unit
Cancer Institute
278 William Street
Melbourne, Australia

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A COMPUTER DOSIMETRY SYSTEM FOR RADIUM IMPLANTS*

By JOSEPH A. ROSE, B.S., FERNANDO G. BLOEDORN, M.D., and J. EUGENE ROBINSON, Ph.D.
BALTIMORE, MARYLAND

ADVANCEMENTS in modern electronic computer techniques have presented to the field of radiotherapy a useful tool, the capabilities of which are just beginning to be exploited in radiation dosimetry. One area where computer techniques are particularly applicable and where more accurate knowledge is badly needed is that of the dosimetry of complex interstitial radium implants. In the last few years, systems have been developed in which computers are used to perform the calculations which describe the radiation fields resulting from such implants. Although the logical techniques and the methods of calculation for these various systems differ, the calculations are of sufficient accuracy for general agreement in clinical dosimetry.

A major consideration in developing a system of this type is the choice of an appropriate form for output data. To be of practical value, the output must be in a form which is easily understood by the clinician who, in the final analysis, makes the decision regarding patient treatment. Because of the very nature of interstitial radium implants, the radiation field varies rapidly with distance; therefore, a tremendous amount of numerical data is necessary to accurately specify their radiation fields. The radiotherapist often has neither the time nor inclination to digest and apply these data to the patient under treatment. He is, however, accustomed to interpreting isodose curves; therefore, isodose curves would appear to be the most natural form for output data. Recently, computer driven plotting devices have been improved to a point whereby they are practical, and we have applied one of these (a Calcomp Digital Incremental Plotter) to translate the numerical data describing com-

plex radiation fields into graphic form.

In clinical application, there often exists a need to calculate the radiation delivered to several planes throughout an implant—planes not necessarily parallel nor with fixed inter-planar spacings. In our institution many radium implants consist of two or more geometrical arrangements of needles,^{1,2} so that it becomes necessary to calculate the dose rate on planes which lie above or below the ends of the needles; e.g., a volume above a plane (Fig. 5). The system here described is general enough that this can be done.

THE SYSTEM IN GENERAL

Briefly, the system is as follows: An IBM 7094 computer system uses the Sievert integrals to calculate the dose rate at discrete points about the various types of radium needles in our stock and permanently stores these dose rates in the form of tables on magnetic tape. The position of points in the vicinity of a radium needle is defined by spherical coordinates as shown in Figure 1. D extends from 0 to 10 cm. in 1 mm. increments and θ extends from 90° to 0° in 1° increments. The radiation field for a needle is thus defined by a 101×91 numerical array. These precalculated tables are then used to calculate the radiation field due to any combination of radium needles placed in any geometrical arrangement by summing, point by point, the radiation intensities stored in the single-needle tables. The resulting numerical data are utilized by a Calcomp Digital Plotter to draw a clear and concise isodose plot of the radiation field in the desired plane along with a "picture" of the needles comprising the implant.

* From the Division of Radiotherapy, Department of Radiology, University of Maryland Hospital, Baltimore, Maryland.

THE FIELDS PRODUCED BY SINGLE NEEDLES

For purposes of calculation, it is convenient to divide the region around a cylindrical radium source of uniform linear density into four different zones. These zones correspond to those described by Sievert^{3,4} in his original formulation of the problem and are shown in Figure 2.

The equations describing the radiation intensity at points within the four zones are:

Zone 1. This zone corresponds to those points where the radiation from all the radium is filtered obliquely through the side of the needle. The dose rate R_p , expressed in rads/hr., at any point $P(D, \theta)$ in the vicinity of a 1 mg. radium source of active length AL , is given by

$$R_p = \frac{8.81}{H \times AL} \int_{\phi_1}^{\phi_2} e^{-0.105/\cos \phi} d\phi, \quad (1)$$

where ϕ_1 , ϕ_2 and H are shown in Figure 2. The constant, 8.81, is the specific γ -ray constant of radium corrected back to zero filtration⁶ and 0.015 is the effective absorp-

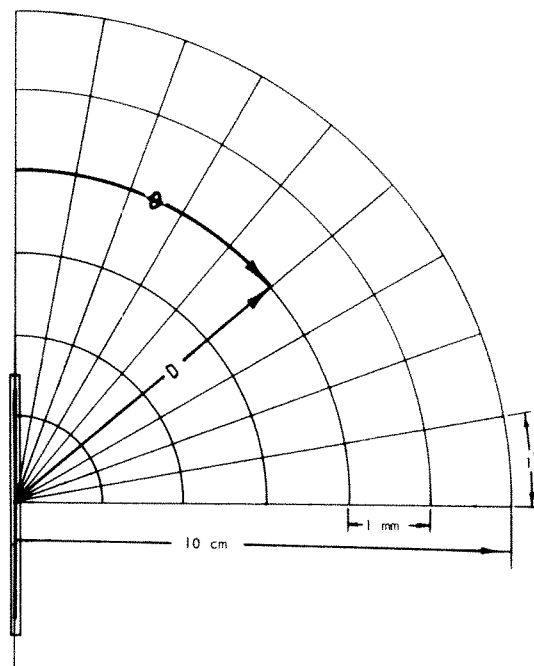


FIG. 1. Spherical coordinate system used to define the position of points in the vicinity of a linear radium source.

Zone 3. This zone corresponds to those points where the radiation is filtered obliquely through the end of the needle (Fig. 2).

$$R_p = \frac{8.81}{H \times AL} \int_{\phi_1}^{\phi_2} e^{[0.1(D \cos \theta - AL/2) - 1.16(TL - AL/2)]/\sin \phi - 0.1 D \sin \theta / \cos \phi} d\phi. \quad (3)$$

tion exponent for a 1.65 mm. diameter needle with 0.5 mm. platinum wall thickness.⁶

Zone 2. This zone consists of a combination of Zones 1 and 3, *i.e.*, part of the radiation is filtered obliquely through the side of the needle and part is filtered obliquely through the end of the needle (Fig. 2). Consequently, the equation describing the dose rate at points throughout this zone is a combination of the equations governing Zones 1 and 3 with the proper limits of integration applied.

TL is the total length of the needle, 1.16 cm.⁻¹ is the effective absorption coefficient of platinum for a thickness of 0.5 cm.,⁶ and 0.1 cm.⁻¹ is the absorption coefficient of radium salt (see later discussion).

Zone 4. This zone corresponds to those points where the radiation is filtered directly through the radium itself and through the end of the needle (Fig. 2).

$$R_p = \frac{8.81}{H \times AL} \left[\int_{\phi_1}^{\phi_2} e^{-0.105/\cos \phi} d\phi + \int_{\phi_1}^{\phi_2} e^{[0.1(D \cos \theta - AL/2) - 1.16(TL - AL/2)]/\sin \phi - 0.1 D \sin \theta / \cos \phi} d\phi \right]. \quad (2)$$

$$R_p = \frac{0.1 \times 8.81}{AL} e^{0.1(D-AL/2)+1.16 \times 0.5(AL-TL)} \int_{0.1(D-AL/2)}^{0.1(D+AL/2)} dX/X^2 e^X. \quad (4)$$

Since radium emits γ -rays of several energies and the radium and needle sheath selectively absorb the lower energies, the effective energy of the radiation will vary with the thickness of the absorber traversed. Thus, the absorption coefficient of the sheath is not a constant but decreases with increasing absorber thickness. Young and Batho⁶ have studied these effects in some detail and their data indicate that this decrease is important only towards the end of the radium source. For our purposes, it appears as though no appreciable error is introduced if we adopt a single appropriate value for the product of the effective wall thickness and the effective absorption coefficient for Zone 1 and a smaller value for Zones 3 and 4, where the thickness of the platinum between the external point and the radiation source is somewhat greater.

In Zone 1, the effective absorption exponent ($\mu_{eff}\tau_{eff}$) is assumed to be 0.105, corresponding to a needle diameter of 1.65 mm. and a wall thickness of 0.5 mm. In Zones 3 and 4, an effective absorption coefficient (μ_{pt}) of 1.16 cm.⁻¹ is used which corresponds to 0.5 cm. of platinum, the approximate thickness of platinum between the active and dead ends of the radium needles in stock. As shown in equation 2, effective coefficients from both Zone 1 and Zone 3 are used in Zone 2 and the transition from zone to zone is continuous.

There is little information available in the literature regarding the absorption coefficient for radium γ -rays in radium salt itself. Young and Batho assume that the linear absorption coefficient for radium is 0.1 that for platinum (based on a packing density of 1.5 gm. of radium per cc.) and suggest that this may be too large for low intensity needles. Our approximate calculations yielded a value of 0.1 cm.⁻¹. The criticality of this value was tested by evaluating the expressions in which it is involved (equations 2, 3 and 4 applying to

those points towards the end of the needle). A variation in values from 0.08 to 0.12 introduced a difference from 1 to 2 per cent. Knowledge of the physical shapes of the ends of the needles, such as the eye and the point, is uncertain. Since this uncertainty would probably introduce greater errors than the value chosen for this constant, we feel that an exact value of this parameter is not critical. A value of 0.1 cm.⁻¹ was therefore used. The effect of tissue absorption and scattering is taken into consideration by using values from Wootton and co-workers⁵ tissue absorption table and interpolating linearly for points which lie between their published values.

None of the above functions can be integrated in finite terms; hence, Simpson's Rule for numerical integration was used. Sufficient accuracy is obtained by using approximately 1 degree increments in applying this numerical method.

The numerical arrays describing the radiation field about a needle are generated as follows: Starting with the point located at $D=0.0$ cm., $\theta=90^\circ$ (Fig. 2) and using the geometry of the zones, the computer

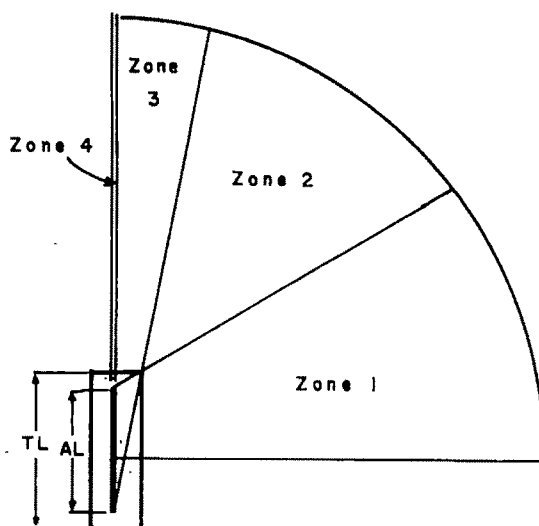


FIG. 2. Various zones of calculation surrounding a linear radium source.

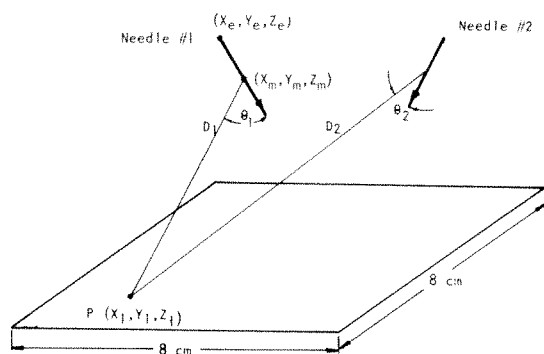


FIG. 3. Diagrammatic representation of a 2 needle radium implant and an arbitrary "plane of calculation."

decides within which zone this particular point lies. It then calculates the dose rate at this point using the appropriate Sievert Integral and stores the value in a table in core storage. If the point falls physically inside the needle, the dose rate is arbitrarily set to 99 rads/hr. Adding 1 mm. to D and holding θ at 90° , it repeats the above procedure and continues until $D=10.0$ cm. One degree is now subtracted from θ and the

above procedure is repeated. This entire process continues until $\theta=0.0^\circ$ and $D=10.0$ cm., thus forming a 101 by 91 array for the needle. Each element of this array specifies the dose rate for a particular point in the radiation field. The array is then transferred to magnetic tape, forming a permanent table for use in subsequent calculations. In this manner, the radiation fields for all uniformly loaded needles in our stock were computed and permanently stored on magnetic tape.

The technique used to calculate and store the radiation fields for "Dumbbell" radium needles is similar to that used for the uniformly loaded needles. Since a "Dumbbell" needle has extra loading at each end, it is convenient to consider the active length of the needle to be made up of three separate segments and apply the appropriate Sievert Integrals to each segment, with proper weighting to account for the differential loading. The same formulae apply, provided the proper limits of integration and linear densities are used.

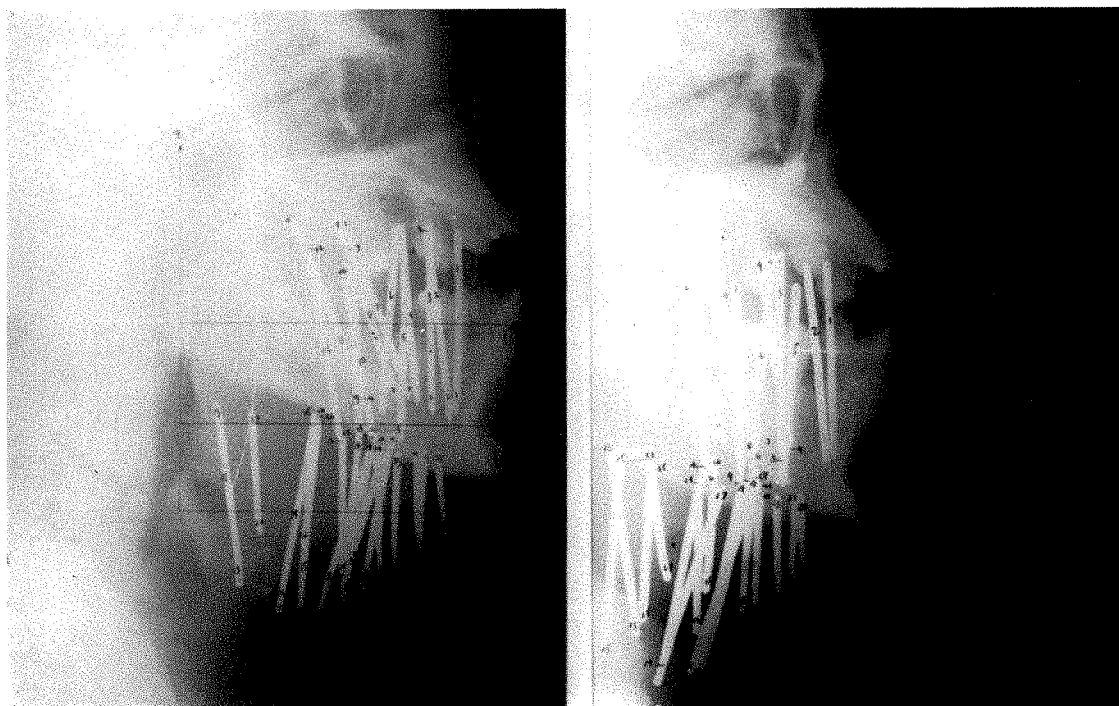


FIG. 4. Stereo roentgenograms used to obtain the computer input data. The radiation field produced by this radium implant is shown in Figure 5.

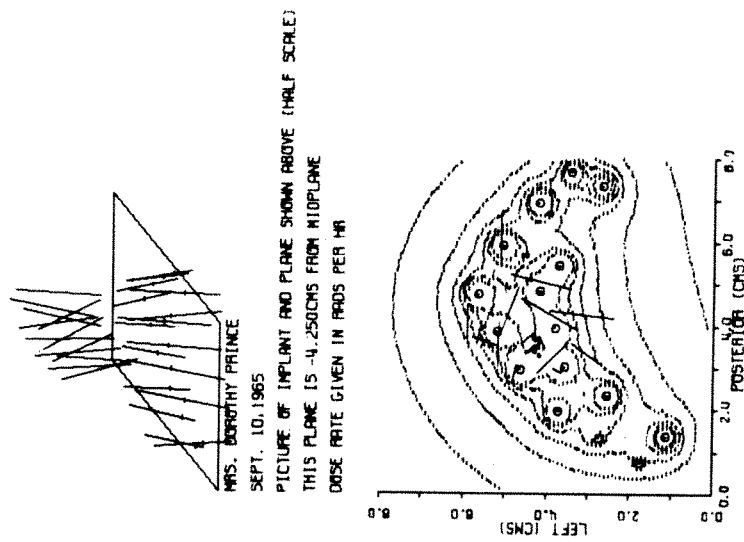
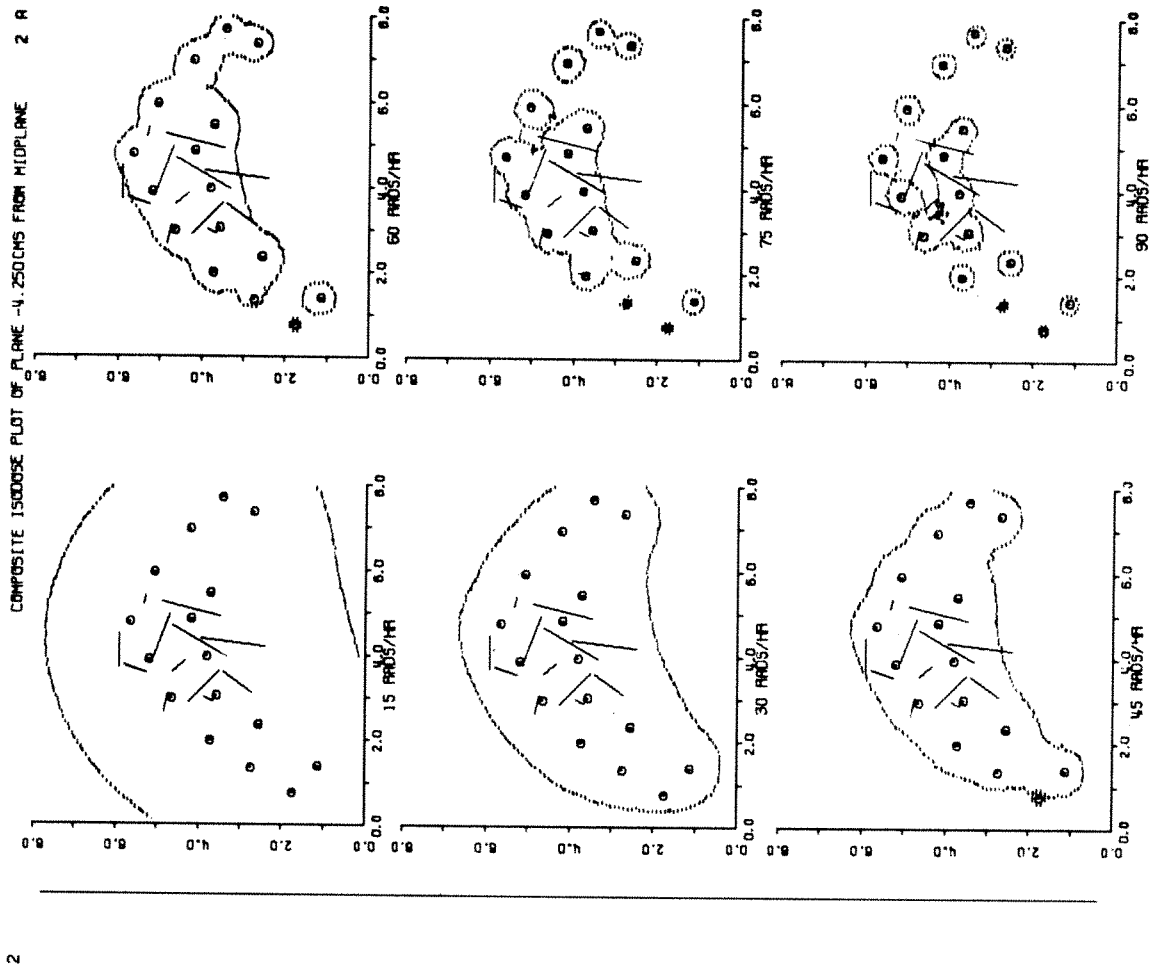


FIG. 5. The computer output drawn by a Calcomp Digital Plotter.

An "Indian Club" needle has extra loading at one end only, and thus does not have the symmetry of either the uniformly loaded, or "Dumbbell" needles. This makes it necessary to calculate the dose rate in two quadrants rather than one, which was possible with the more symmetric arrangement. Here, the active length was divided into two segments and the corresponding integrals were weighted to account for the extra loading. To keep the permanently stored dose tables in the form of a 101 by 91 array, the dose rate was calculated using 2 degree increments instead of 1 degree increments.

THE FIELDS PRODUCED BY MULTIPLE NEEDLES

The system is designed to calculate the radiation field on any plane throughout the implanted region and these planes are chosen by the radiotherapist for clinical interest. Because of practical considerations, such as computer time and implant size, the planes of calculation are limited to an 8.0 cm. by 8.0 cm. field. The dose rates are calculated at discrete points along a 1 mm. grid (6,400 pt. per plane) and are used to define the isodose curves.

The relative positions of radium needles in space are defined by the coordinates of the needle endpoints. To obtain these coordinates, a set of stereo roentgenograms are taken of the implant region (Fig. 4). In one, the central x-ray beam is perpendicular to the film cassette, and in the other, the central x-ray beam is oblique to the cassette. In taking these roentgenograms, we use a 1:4 ratio of tube shift to focus film distance which is a reasonable optimum for data accuracy. For greatest accuracy, a large focus film distance and image shift are desirable, and from practical considerations a focus film distance of 150 cm. and a tube shift of 40 cm. were adopted. For the endpoints of each needle, two coordinates are obtained from the perpendicular film and the third is calculated from the image shift. Magnification corrections for each individual needle are made using the coordinates of the needles

obtained directly from the perpendicular roentgenograms. For a given implant, the accuracy of the output is limited by the accuracy of the input data. It is our feeling that the computational accuracy available with computer techniques justifies some efforts being made to obtain accurate input data. To do this, techniques were developed to accurately and easily reproduce the focal film distance, tube shift, and focal spot position relative to the film. As a check on accuracy, the coordinates of the needle endpoints are used to calculate the total needle length. These values, together with the actual length, are part of the output data. In general, the computed total length agrees with the actual length within 1 to 2 per cent (Fig. 5).

After the roentgenograms for a particular patient have been taken, the "initial plane of interest" is chosen and the input data are recorded. From these input data, the cartesian rectilinear coordinates of the endpoints of the needles relative to this initial plane are calculated by the computer. Using the description (*AL*, *TL*, etc.) of the first needle in the implant, the computer searches the permanent storage tape for the dosage table corresponding to this needle. This table is read into core storage from which data can rapidly be retrieved. The machine is now ready to determine the dosage contribution of the first needle to the initial plane of interest. Starting with Point 1 (Fig. 3) the following quantities are calculated:

1. The distance (*D*) from the first point on the calculation plane $P(X_1, Y_1, Z_1)$ to the center of the first needle.

$$D = \sqrt{(X_1 - X_m)^2 + (Y_1 - Y_m)^2 + (Z_1 - Z_m)^2} \quad (5)$$

2. The angle (θ) between the axis of the needle and the line joining the first point $P(X_1, Y_1, Z_1)$ to the midpoint of the needle.

$$\theta = \cos^{-1} \left| \frac{X_1 X_2 + Y_1 Y_2 + Z_1 Z_2}{0.5 \times D \times TL} \right| \quad (6)$$

Since the permanent storage tables contain the dose rate at points in the vicinity of

a single needle (defined in term of D and θ) and the table for the first needle is already in core storage, the computer can retrieve the dose rate (R) corresponding to the value of D and θ just calculated and store it (R) as the dosage contribution to Point 1 from this needle. The computer then repeats the procedure for Point 2 and in like manner for all 6,400 points. The table for the second needle is now placed in core storage and the dose contribution for Needle 2 is added point by point to that from Needle 1. This procedure is repeated for each needle in the implant forming a dosage table for this plane. This calculated table (6,400 points) describes the radiation field for the plane and is available for subsequent operations. Storage capabilities of the computer limit the total number of needles to 40. The computer now calculates the position on this plane of isointensity points for 15, 30, 45, 60, 75 and 90 rads/hr. The positions of the intersection of needles with this plane are also calculated and stored. For those needles which do not intersect the plane, the projections of the endpoints of the needles onto the plane are stored. Using Calcomp subroutines, the data are placed in the proper format and stored on a "plot tape," which will later be used to drive the plotter. The machine is now ready to compute the radiation field for other planes in the vicinity of the implant.

To calculate the radiation field on a parallel plane, for example 1.0 cm. above, the Z coordinate of the plane of calculation is changed from 0.0 cm. to 1.0 cm. (part of the input data) and the entire process is repeated. To calculate the field for planes which are not parallel to the "initial plane," the coordinates of the needles are appropriately rotated and translated to define a new plane of calculation relative to the implant. The entire dose calculation procedure is now repeated, completing the necessary calculations for the implant. The "plot tape" is now removed from the computer and placed on the plotter which draws the isodose curves. Figure 5 demonstrates the plotter output which includes:

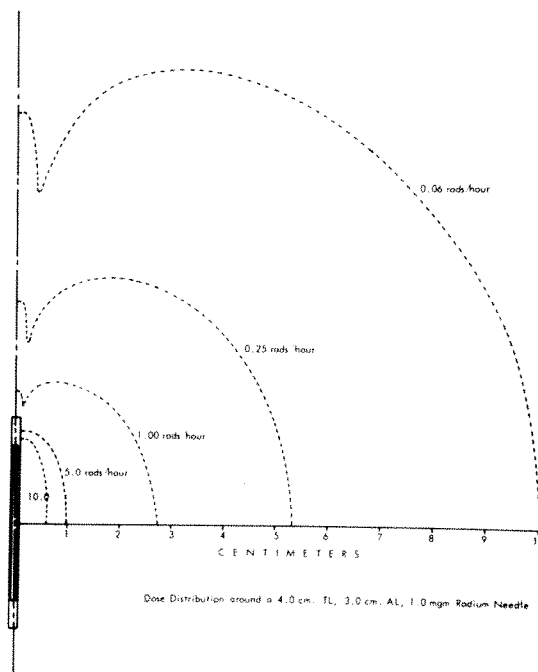


FIG. 6. The radiation field produced by a finite linear radium source calculated using 4 zones.

- a full size plot of 6 isodose lines chosen for clinical interest to be 15, 30, 45, 60, 75 and 90 rads/hr.;
- the position of the needles which intersect the isodose plane;
- the projection on this plane of crossing needles or other needles which do not intersect this plane;
- an oblique drawing of the implant and plane of calculation drawn half scale;
- a list of the needles in the implant along with the computed total length of the individual needles comprising the implant; and
- finally, pertinent patient data such as patient name, date of implant, etc.

As an example of computer time required, a 20 needle implant requires approximately 2 min./plane to calculate and approximately 5 min./plane to plot. All computing and plotting facilities are made available by the University of Maryland Computer Science Center, College Park, Maryland.

SUMMARY

A system has been developed to calculate and plot the radiation fields produced by radium needle implants. An IBM 7094 computer system is used to perform the necessary calculations and a Calcomp Digital Incremental Plotter is used to place the data in graphic form. A program was written which uses the four Sievert Integrals to calculate and permanently store on magnetic tape the data describing the radiation fields around the various single needles in our stock. A second program utilizes these precalculated tables to compute and plot the radiation fields around radium implants. The system is versatile enough to allow for the computation and plotting of the radiation fields on any planes in any position in the vicinity of a radium implant.

Joseph A. Rose, B.S.
Department of Radiology
University of Maryland
School of Medicine
Baltimore, Maryland 21201

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A NOMOGRAM FOR COBALT 60 TELETHERAPY CALCULATIONS*

By BAHMAN MOHTASHEMI, M.D.
BOSTON, MASSACHUSETTS

CALCULATION of treatment time in cobalt 60 teletherapy is a time consuming procedure. It is desirable, especially in a busy department, to use a calculator which will give the treatment time and related values immediately with negligible error. For this purpose, several nomograms and calculators have been devised in recent years.^{2,4,5,6} The purpose of the author is to describe a nomogram for cobalt 60 teletherapy by which the treatment time, maximum equilibrium dose (M.E.D.) and exit dose for all source-skin distances (S.S.D.) and with different areas, and a correction factor for cobalt 60 decay can be calculated.

This nomogram is shown in Figure 1. In its present form, it is adjusted for a machine with an output of 50 r in air at 1 meter S.S.D. and a 100 cm.² area. Adjustment for other outputs will be discussed later. It consists of 5 major scales: Scale A = tissue depth in centimeters; Scale B = dose in rads; Scale C = surface areas in cm.² at different source-skin distances in centimeters; Scale D = treatment time in minutes and seconds; and ungraded Scale E = dose rate.

I. USE OF THE NOMOGRAM

Calculation of the treatment time is made in the following manner:

Put the nomogram on a smooth surface. Place a ruler on the paper so that its edge is on the tumor depth on Scale A and on the field size on the corresponding S.S.D. curve on Scale C. Put the sharp point of a pencil at the intersection of the edge of the ruler and Scale E and hold it. In the second step, while the pencil is held fixed in place, move the ruler so that it always touches the tip of the pencil, mark off the tumor dose in rads on Scale B with the other side, and in

this position, read off the treatment time at the intersection of the ruler and Scale D.

Knowing the treatment time, the maximum equilibrium dose (M.E.D.) and exit dose (E.D.) can be calculated.

For calculation of the M.E.D. join 0.5 cm. depth on Scale A and corresponding S.S.D. and area on Scale C with the ruler intersecting Scale E, and in the second step join this intersection and treatment time (determined before); read off the M.E.D. at the intersection of the ruler and Scale B.

For finding the exit dose follow the same steps as for finding the M.E.D. with the difference that in the first step, put the ruler on the corresponding exit depth instead of 0.5 cm.

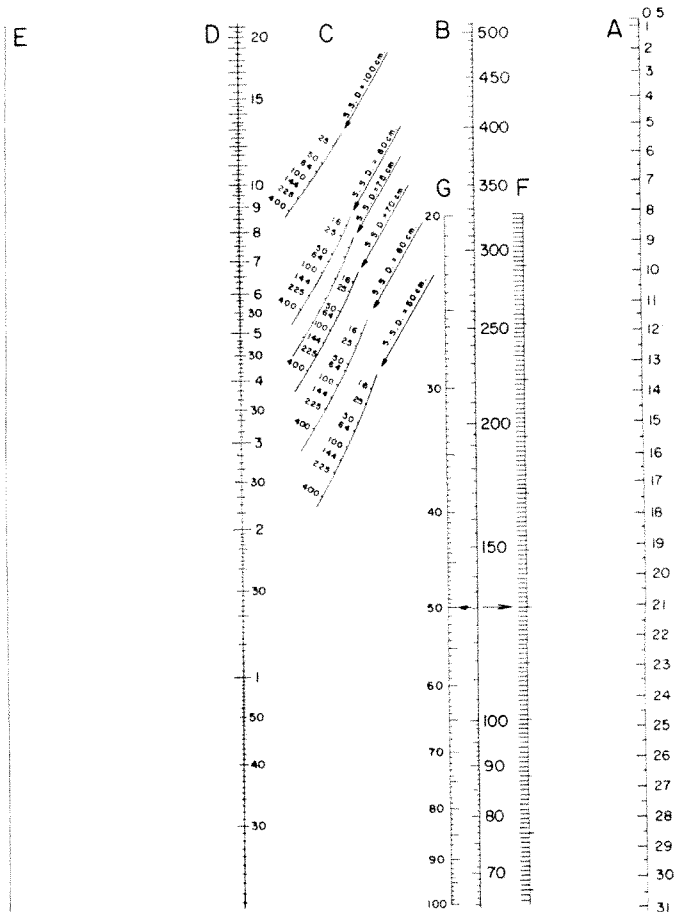
Similarly, the dose at any depth can be determined.

II. THE BASIS OF THE NOMOGRAM

The nomogram is based on the fact that by two successive multiplications we can find the tumor dose. First, multiply the maximum equilibrium dose by the percentage depth dose to find the dose rate, and then multiply the dose rate by the treatment time to find the tumor dose. On this tenet the nomogram has two essential parts. The first part is composed of Scale A which is representative of percentage depth dose, Scale C which represents the M.E.D. at different source-skin distances and areas, and Scale E representative of dose rate. Although the actual figures are not written on these scales, the position of their points on the paper is such that, for each situation, they are equivalent to their actual values. (The values on Scale E are purposely omitted because, due to cobalt 60 decay, they will change during time and need correction. Now, correction can be made only

* From the Department of Radiology, Boston City Hospital, Boston University Medical Center.

FIG. 1. A nomogram for cobalt 60 teletherapy calculations. Scale A=depth of the tumor in cm. Scale B=dose in rads. Scale C=source-skin distances in cm.; surface areas in cm^2 are plotted on each S.S.D. curve. Scale D=time in minutes and seconds; note that this scale increases from below upward and this should be considered during reading. Scale F=monthly decay lines; the intervals of yearly decay are shown by longer lines crossing the vertical line. Scale G=output of the machine (see text); to adjust the nomogram to any machine move Scale B until the arrow is pointed to its output.



by Scale B). The values on Scale E are the product of the values on Scales A and C which are joined together by a straight line. The second part of the nomogram is composed of Scales E, D (treatment time), and B (dose). Scale B always shows the product of the values on Scales E and D which are joined together by a straight line.

The construction of the second part of the nomogram is simple. The values are placed on Scales B, D, and E logarithmically and they function in the same manner as a slide rule.⁶

The construction of the first portion of the nomogram basically follows the same principles; however, due to the involvement of several factors, it is more complicated. In order to be able to construct this portion of the nomogram, the output of the

cobalt 60 machine at different source skin distances and areas should be known. One problem is variation of the output with area, or, in other words, variation of the output with different openings of the collimator due to the scatter from the collimator blocks.^{1,3,7} This variation is dependent on the shape of the blocks and the size of the source³ and is not equal in all machines. For this reason, it is difficult to make one nomogram for all cobalt 60 machines; nevertheless, this variation, more or less has a similar pattern,⁷ and, therefore, a nomogram for one machine can be used, with negligible error, for other machines. This variation is also responsible for the slight shift from the inverse square law.¹ For the present nomogram, the output variation of the Picker machine was assumed to be 14 per cent between 16 and 400 cm^2 areas at

50 cm. S.S.D.⁷ If another machine has, for example, a 10 per cent variation at this range, the highest error would be in the order of ± 3 per cent.

A machine which delivers 50 r at equilibrium condition in air at 100 cm. S.S.D. and 100 cm.² area was assumed as a base. The outputs of such a machine for different source-skin distances and areas were determined. By applying back scatter factors for each area³ and also the factor of rad-roentgen conversion (0.96)³, the maximum equilibrium dose rates of such a machine for all these situations were obtained and were used for finding the points of the curves on Scale C. Now, if Scale A is graded logarithmically for percentage depth dose and for a single situation (for example 80 cm. S.S.D. and 100 cm.² area), corresponding depths are plotted on Scale A, due to the fact that Scale E represents dose rate logarithmically, a given point can be found and, if it is joined to any depth on Scale A, its continuation will intersect Scale E at a proper level which represents the dose rate at that depth. Because the percentage depth dose chart varies with the different source-skin distances and areas, it would appear that for each situation a separate Scale A might be needed. However, due to the fact that the attenuation curves of cobalt 60 in tissue follow closely an exponential pattern, Scale A can be enlarged or diminished in such a way that only one Scale A may be used for all situations provided it has a different logarithmic basis. Therefore, Scale C is not a straight line paralleling the other scales; the points with the higher percentage depth dose values being closer to Scale E and the points of the lower depth dose values being closer to Scale A. To find the points on Scale C, the dose rates were plotted logarithmically on Scale E; by using depth dose charts,³ the dose rates of each point at certain depths were found, and, by joining them from Scale E to their corresponding depths on Scale A by straight lines, the desired points were obtained at the intersection of the lines.

III. DECAY OF THE COBALT 60

The nomogram in its present form is set for a machine with an output of 50 r in air in equilibrium condition at 100 cm. S.S.D. and 100 cm.² area. Due to cobalt 60 decay, the output will change with time and all the values must be multiplied by the cobalt 60 decay factor each month. On a logarithmic scale, in order to correct for this decay, it is enough to raise Scale B a certain constant distance each month.⁶ Since every 5.24 years, or 63 months, the intensity of cobalt 60 is reduced to half, any segment of Scale B representing a change by a factor of 2 (for example, between 100 and 200) should be divided into a total of 63 divisions and each month Scale B should be raised one division. Scale F was designed for this purpose and is divided accordingly. We use a duplicate of Scale B which can be moved up and down but not laterally, and every month we raise it so that the arrow which is attached to it goes up one division on Scale F.

Scale G shows the output of the machine in r in air, at 100 cm. S.S.D. and 100 cm.² area in equilibrium condition. To adjust the nomogram to any machine, if its output is known under these conditions, Scale B should be moved up or down until the arrow points to the correct output on Scale G.

There is another way of adjusting the nomogram. If the maximum equilibrium dose in rads at a certain S.S.D. and area is known, we can join the 0.5 cm. depth on Scale A and the point on Scale C representing that area and the S.S.D. to intersect Scale E, and then join 1 minute (on Scale D) with that intersection by a ruler, while moving Scale B up or down until the edge of the ruler shows the known M.E.D. value. By a similar procedure, if we use the maximum equilibrium exposure in r, we can adjust the nomogram to read in roentgens, instead of rads, if so desired.

On the pattern of this nomogram, a special device can be made which will greatly facilitate its use, by considering two points:

(1) A straight rod in place of Scale E with a transparent ruler attached to it which can have vertical and rotational movements in relation to the rod.

(2) A ruler in place on Scale B which can be moved up and down and be fixed at desired position.

Department of Radiology
Boston City Hospital
Boston, Massachusetts 02118

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THERMOLUMINESCENT DOSIMETRY OF BETA DEPTH DOSE*

By WILLIAM R. HENDEE
DENVER, COLORADO

RADIATION dosimetry utilizing the phenomenon of radiothermoluminescence exhibited by various crystals promises to provide in many clinical and experimental situations a method for obtaining accurate and rapid measurements of absorbed dose. The influence of various physical parameters upon the radiation response of different thermoluminescent powders has yet to be precisely delineated. Nevertheless, the radiothermoluminescent behavior of certain crystals is established sufficiently to permit, at this time, limited dosimetric application under carefully controlled conditions. Measurements of surface and depth dose from commercially available beta applicators used to treat lesions of the eye appear, for at least two reasons, to be particularly amenable to thermoluminescent dosimetric techniques. First, the essentially "tissue-equivalent" composition and relatively energy independent response of commercially available LiF thermoluminescent powder, together with the ease and reproducibility of this measurement technique, suggest advantages of radiothermoluminescent measurements over those made with photographic film. Second, the direct measurement of absorbed dose rather than exposure, together with the simplicity and rapidity of the radiothermoluminescent method, suggests features superior in most cases to extrapolation chamber or thin ionization chamber techniques of measurement. The applicability of radiothermoluminescent methods to the problem of beta dosimetry has been tested in this experiment by comparing beta depth dose data obtained in our laboratory by thermoluminescent measurements with those obtained on similar beta sources by other investi-

gators using film and ionization chamber techniques.

THEORY

When heated to sufficiently high temperatures, certain crystals containing small amounts of impurity have been observed to fluoresce in the visible region following exposure to ionizing radiation.² The amount of fluorescence from a given weight of irradiated crystalline powder appears proportional to the radiation dose. Evidently, electrons are raised above their ground energy state in the crystals by absorption of energy from the incident radiation. Some of these electrons are "trapped" in metastable energy states provided by the impurity atoms in the crystals. By heating the crystals, the trapped electrons can later be freed from the metastable energy states. Upon returning to the ground state, the electrons release their excess energy as visible light. The amount of light released is a function of the number of electrons liberated from the electron traps. At any particular crystal temperature, the number of electrons released from the metastable energy states is a function of the number of electrons trapped in those states. This number is determined by the amount of energy originally absorbed from the incident radiation. The amount of light generated by the returning electrons can be measured with a conventional photomultiplier tube, analog-digital converter, and decade scaling circuits. By proper calibration, this measurement may serve as an index to the energy absorbed or dose received from the incident radiation. Complete thermoluminescent read-out systems are now available commercially.

* From the Department of Radiology, University of Colorado Medical Center, Denver, Colorado.
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PROCEDURE

Approximately 15 mg. of Harshaw TLD-100 LiF powder of crystal diameter between 100 and 200 mesh Tyler (74-149 microns) was spread over a lucite block to uniformly fill a slight depression 0.9 cm. in diameter and less than $\frac{1}{4}$ mm. in depth. The powder had previously been annealed by heating it for 1 hour at 400°C., cooling it rapidly, and then reheating it for 24 hours at 80°C. The powder was covered with 0.04 mm. of polyethylene and exposed to Y^{90} betas by positioning a Tracerlab Sr^{90} - Y^{90} beta applicator of 0.9 cm. active diameter in contact with the upper surface of the polyethylene sheet. For all exposures the period of contact was sufficient to irradiate the powder to a dose between 300 and 800 rads. Absorbed dose measurements at various depths in tissue were obtained by placing selected thicknesses of essentially "tissue-equivalent" lucite of density 1.14 g./cm.³ between the beta source and the LiF powder. Following each exposure, the powder was carefully collected and stored for 48 hours. The fluorescence from equal amounts (approximately 30 mg.) of heated powder was determined with a Madison Research and Development Laboratories Model S-2 thermoluminescence radiation exposure meter. A maximum temperature of 232°C. was attained during the read-out cycle.

The measured fluorescence was calibrated as a function of absorbed dose by exposing the radiothermoluminescent powder to gamma radiation from a cobalt 60 teletherapy unit. Since preliminary studies in this laboratory suggest that the fluorescence response of LiF to ionizing radiation is dependent to a small degree on dose rate, the calibration was performed at a dose rate (17.0 ± 0.2 rad/sec.) similar to those encountered during exposure to the beta source ($\leq 19.2 \pm 0.6$ rad/sec.). Calibration of fluorescence versus dose with cobalt 60 gammas appears justifiable since calculations indicate that the average Compton electron energy from these gam-

mas (roughly 0.6 mev.) is fairly near the average beta energy from Y^{90} (0.93 mev.). Brownell¹ has noted that the average beta energy does not change significantly during absorption. The applicator is designed to absorb the lower energy Sr^{90} betas and transmit only the higher energy Y^{90} betas. Studies by Kastner and Hukko⁴ using various beta sources suggest that the thermoluminescent response of LiF is essentially independent of electron energy for all but the lowest energy betas. Fluorescence of the powder exposed to Co^{60} gammas was determined 48 hours following exposure in a manner identical to that used with the beta-exposed powder. The entire experiment was performed with LiF obtained as a single batch from Harshaw Chemical Company. During exposure to cobalt 60 gammas, the LiF was contained within 5.0 mm. O.D., 15 mm. long teflon capsules enclosed in an equilibrium shell of 300 mg./cm.² lucite. Dose rate at the position of exposure of the LiF to cobalt 60 gammas was determined with a Victoreen high energy condenser chamber calibrated against an identical NBS-calibrated chamber.

RESULTS AND DISCUSSION

The thermoluminescence of LiF used in this experiment as a function of radiation dose is tabulated in Table I and demonstrated in Figure 1. The response of the crystalline powder is not quite a linear function of absorbed dose, exhibiting a slightly increasing slope over the entire range of dose which is particularly noticeable at the higher doses. The mean counts and their standard deviations listed for each dose in Table I were calculated from between 17 and 21 separate fluorescence measurements. The precision of the measurements is suggested by the fact that in no case does the standard deviation exceed 1.7 per cent of the mean.

Results of the radiothermoluminescence measurements of beta depth dose are listed in Table II and illustrated by the solid line in Figure 2. The standard deviation of each

TABLE I

THERMOLUMINESCENT RESPONSE OF HARSHAW TLD-100 LiF AS FUNCTION OF ABSORBED DOSE

Dose (rads)	Mean Counts
317	$2,731 \pm 34$
522	$4,632 \pm 54$
727	$6,754 \pm 80$
829	$7,736 \pm 68$
931	$8,832 \pm 112$
1,133	$10,965 \pm 188$
1,340	$13,663 \pm 142$

measured depth dose was calculated from at least 14 separate exposures to Y^{90} betas. The difficulty in providing a uniform LiF layer of consistent thickness, together with the meticulous care necessary to collect all the exposed powder granules, probably account for the lower precision of these measurements as compared to those obtained during the cobalt 60 calibration. Nevertheless, the standard deviation in no case exceeds 6 per cent of the mean depth dose and in most cases is much lower.

Included with the thermoluminescent data in Figure 2 are depth dose data on similar beta sources obtained by different methods. The dash-dotted curve labeled Supe and Cunningham⁵ and almost coincident with the solid line describing the thermoluminescent data represents extrapolation chamber measurements of Y^{90}

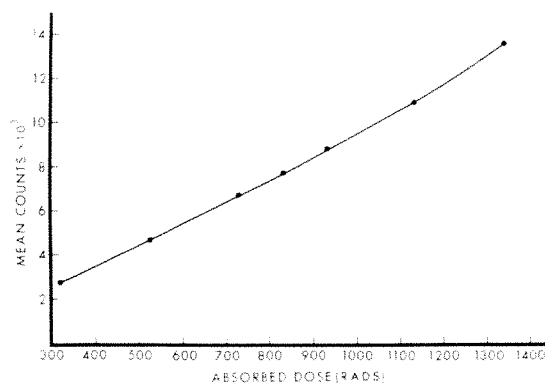


FIG. 1. Thermoluminescence of Harshaw TLD-100 LiF as a function of absorbed dose from Co^{60} gamma radiation.

TABLE II

 Y^{90} BETA DEPTH DOSE DATA

Absorber Thickness (mg./cm. ²)	Per Cent Depth Dose
Surface	100.0 ± 2.7
57	70.6 ± 1.7
114	50.0 ± 1.9
228	24.1 ± 1.2
365	9.67 ± 0.61
456	4.17 ± 0.11

beta depth dose. The good agreement between the extrapolation chamber measurements and the data obtained in the present experiment is apparent. The lower dashed curve labeled Tochilin and Golden⁶ and the lower dotted curve labeled Freitag *et al.*³

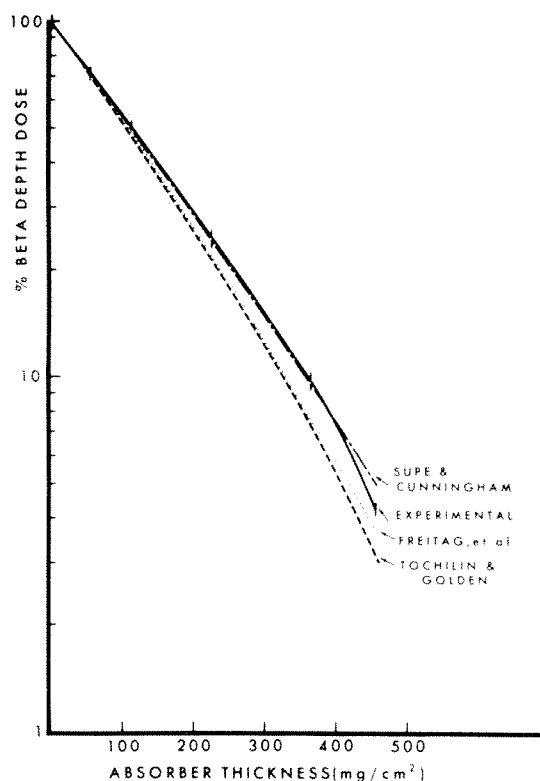


FIG. 2. Comparison of Y^{90} beta depth dose curves obtained by thermoluminescence (solid line), film (dotted and dashed lines), and extrapolation chamber (dash-dotted line) techniques.

represent data obtained by densitometric measurements of the blackening of film exposed to Y^{90} betas. The slightly more rapid fall-off in dose indicated by the film measurements may be due, at least in part, either to the higher effective atomic number of film or to inaccuracies such as energy dependence and variations in development inherent in film dosimetry. This slight discrepancy between the two methods is in essential agreement with comparative studies performed by Tochilin and Golden. In any case, the good agreement between the thermoluminescent measurements of beta depth dose and data obtained on similar sources by other techniques implies the usefulness and accuracy of this approach to problems of measuring relative absorbed dose.

SUMMARY

Radiothermoluminescent measurements have been made of Y^{90} beta depth dose from a commercially available Sr^{90} - Y^{90} beta applicator. Good agreement of the resulting beta depth dose curve with those obtained by film and extrapolation chamber techniques of measurement suggests the usefulness of radiothermoluminescent dosimetry as a rapid and convenient ap-

proach to the measurement of relative absorbed dose.

Department of Radiology
University of Colorado Medical Center
4200 East Ninth Avenue
Denver, Colorado 80220

The author wishes to express his thanks for use of equipment to Dr. Carlos Garciga and to Mr. Robert Golden.

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CHANGES IN THE RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) OF A 35 MEV. ELECTRON BEAM AS A FUNCTION OF TISSUE DEPTH*

By GEORGE SCHWARZ, M.D., ROGER BERG, M.D., and CHARLES BOTSTEIN, M.D.
BRONX, NEW YORK

ZIRKLE and Tobias⁵ first demonstrated that the biological effectiveness of an electromagnetic or corpuscular radiation is not one of its intrinsic properties, but rather a function of the rate of linear energy loss (dE/dx) along radiation tracks in tissue. This linear energy transfer (LET) defines the amount of energy deposited in the immediate vicinity of the primary ionizing tracks by the production of secondary electrons of low energy.

It has also been shown that there exists a close relationship between LET and relative biological effectiveness (RBE) (Fig. 1). A logarithmic increase in LET is usually associated with a linear increase in RBE with maximum biological effectiveness occurring between LET values of 100 and 200 kev./ μ .

LET increases with increasing particle size and decreases with higher energies. A minimum value of about 0.1 kev./ μ occurs at x-ray and β energies of 0.51 mev. (Fig. 2).

With x- or γ rays the energy distribution of secondary electrons is more or less uniform throughout the irradiated volume. A primary high energy electron, however, produces relatively few ionizing events along the initial and greatest portion of its path, giving rise to a high ion density only when it is degraded to an energy of less than 0.5 mev. in the last 2 mm. of its path. The low energy secondary electrons, or δ particles, are believed to be biologically more effective than the primary particles because of their lesser energy and higher LET. Wideröe postulates that cell death occurs only when the energy released in the sensitive volume exceeds a minimum value, e.g., 750 ev. This means that only δ elec-

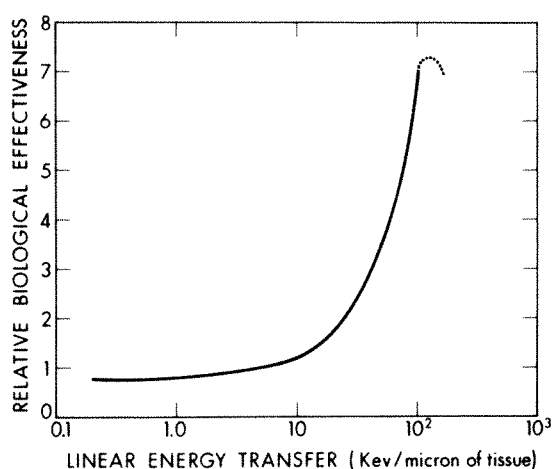


FIG. 1. Graph demonstrating log-linear relationship between linear energy transfer (LET) and relative biological effectiveness (RBE). The closest correlation occurs in the therapeutic range (7-30 kev./ μ). The reversal of the curve past the maximum probably represents a saturation effect (drawn after Fowler, Bewley, Barendsen and Walter).

trons with energies above 750 ev. (*i.e.*, occurring in the last 0.04 μ of the primary electron track) are biologically important.⁴

Regions of increased δ particle density in a tissue irradiated by a beam of high energy electrons may, therefore, be of interest in radiation therapy. Wideröe has calculated the existence of such a region near the end of the primary electron tracks (Fig. 3). Since impinging electrons are stopped at various depths in tissue, δ particles are distributed throughout the entire irradiated volume but will be relatively concentrated at the level where dose falls sharply, *i.e.*, where many primary tracks end (Fig. 4). The number of δ electrons in this region is high and LET and RBE both rise accordingly (Fig. 5). Haynes and

* From the Department of Radiotherapy, Montefiore Hospital and Medical Center, Bronx, New York.

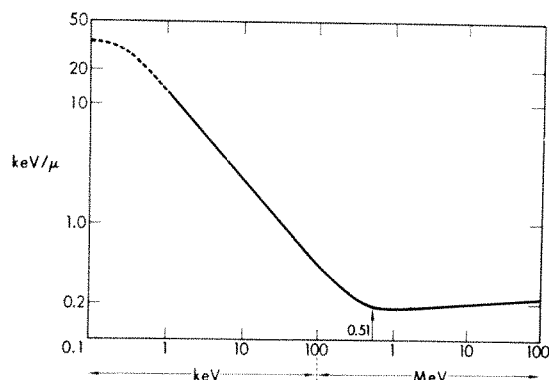


FIG. 2. Inverse log-log relationship between LET (keV./ μ) and radiation energy applies to both β and γ radiation (after Markus and Sticinsky²).

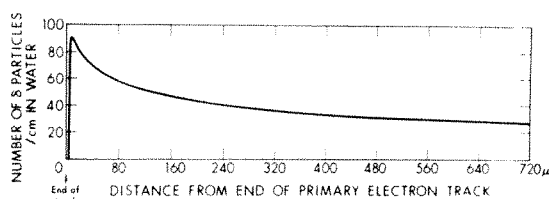


FIG. 3. The number of secondary δ electrons rises sharply as the primary electron approaches the end of its track; δ particle density will thus be highest at the depth where many primary electron tracks end (after Wideröe⁴).

Dolphin¹ have calculated a rise in LET from 7.4 keV./ μ in the plateau region to 30 keV./ μ in the terminal portion of a 14 mev. electron beam (Fig. 6).

Laboratory confirmation of these findings has produced conflicting results. The purpose of our work was to demonstrate the increase in LET calculated by Haynes and Dolphin.¹ Because of the close relationship between LET and RBE at relatively low LET values, it was felt that a change in the former would accurately be reflected by a change in the latter.

METHOD

Ten week old CF₁ male mice were given total body irradiation at various depths of a lucite phantom³ with doses ranging from 600 to 1,500 rads with the 35 mev. electron beam of a Brown-Boveri betatron. Death rates were recorded and isoeffect doses compared. Since the calculated zone of in-

creased δ particle production (and increased RBE) measures several centimeters in depth, the size of the test object was not thought to be critical in revealing its presence. Although a 2 to 3 per cent absorbed

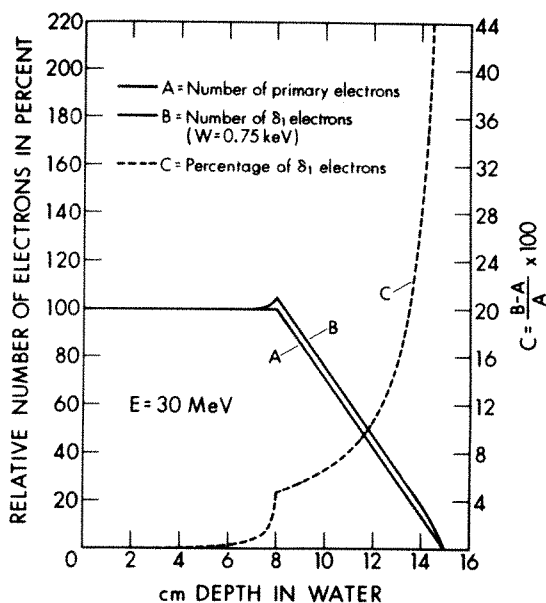


FIG. 4. The relative proportion of δ electrons increases sharply as the number of primary electrons diminishes more rapidly than the δ electrons they have produced (after Wideröe⁴).

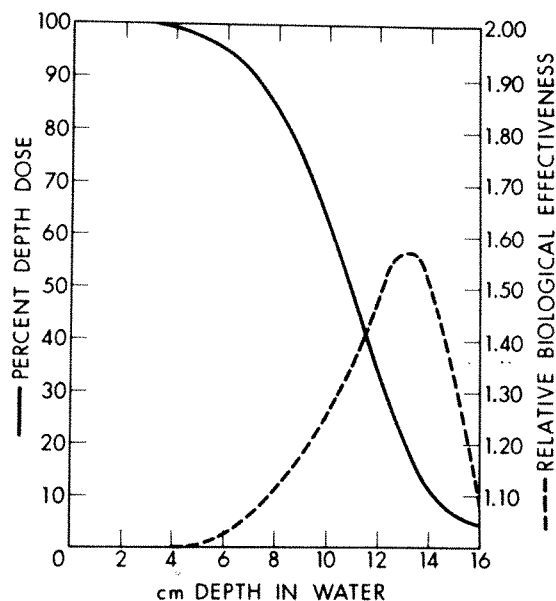


FIG. 5. RBE curve calculated as a function of δ particle density at various depths (after Wideröe⁴).

dose variation may occur across the 2 to 2.5 cm. width of the animal because of the rapid fall-off of electron dose rate, this was assumed to be unimportant in comparison to the magnitude of the RBE change that we expected to demonstrate. Furthermore, we believed that dose inhomogeneities occurring at tissue interfaces of different density would be quantitatively less important in a large biological test system than in a small one.

Our experimental design was as follows: Nine hundred 10 week old CF₁ mice were divided into 3 identical groups and irradiated at various depths of a lucite phantom. These were at the 100 per cent (maximum), 60 per cent and 12 per cent isodose levels. One hundred additional mice served as controls and were given sham irradiation (Fig. 7).

The animal irradiation chamber was also made of lucite, with cylindrical individual animal compartments measuring 2.5 cm. in diameter to minimize any intervening air space. Dose determinations were made with a ferrous sulfate dosimeter, the solution in the test tube being irradiated at the center of the compartment within the abdomen of a freshly killed animal. Readings were similarly obtained with a Baldwin-Farmer ionization chamber and lithium fluoride rods. Absorbed dose rate was kept within a relatively small range, measuring

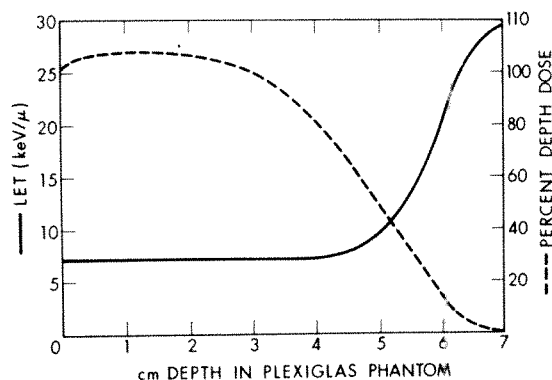


FIG. 6. Calculated LET curve as a function of depth in a water phantom irradiated by 14 mev. electrons. LET rises in the region of sharp dose fall off (after Haynes and Dolphin¹).

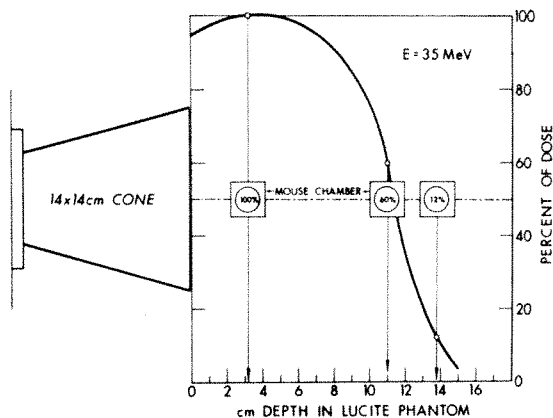


FIG. 7. Schematic representation of experimental mouse irradiation set-up. Animals were irradiated at doses varying from 600 to 1,500 rads at various depths of a lucite phantom.

45 rads/min. at the 12 per cent isodose level and about 90 rads/min. at the 60 per cent and 100 per cent levels.

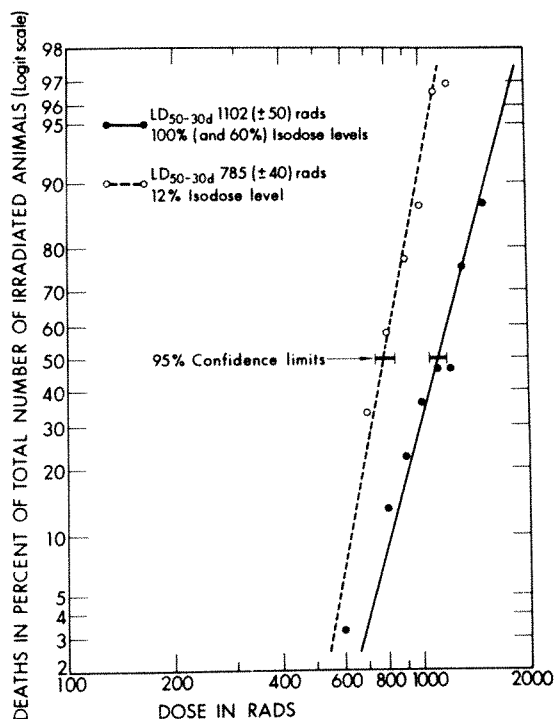


FIG. 8. Survival curves showing increased lethality of electrons at 12 per cent isodose level as compared to 100 per cent and 60 per cent levels. No differences could be demonstrated between these two latter isodose regions. Note difference in survival curve slope.

Groups of 30 animals were irradiated at each dose level, ranging from 600 rads to 1,500 rads in 100 rad increments; one-half of the total dose was given to each side of the mouse. Deaths occurring within 30 days were included in the tabulation.

RESULTS

The LD 50/30d was identical at the 100 per cent and 60 per cent levels. The dose-response curves at these depths could be superimposed. At the 12 per cent level, however, the LD 50/30d was reduced by a factor of 1.48, and the slope of the dose-response curve was steeper than at the other levels (Fig. 8).

LD 50/30d		RBE
100% level	1,100 rads	1
60% level	1,100 rads	1
12% level	740 rads	1.48

SUMMARY

Survival curves obtained by *in vivo* total body irradiation of young CF₁ mice indicate a change in the RBE of 35 mev. electrons as they penetrate through tissue. The results are in agreement with those of Markus and Sticinsky² and with the calculations of Haynes and Dolphin¹ in that they

suggest a long plateau region of low LET followed by terminal rise. They indicate a minimal three-fold increase in the terminal portion LET as compared to the plateau region if the log-linear relationship between LET and RBE holds. The relatively large cross-section of the test object may have concealed an even higher RBE peak. Studies using a smaller test object are now in progress.

George Schwarz, M.D.
Department of Radiotherapy
Montefiore Hospital and Medical Center
Bronx, New York 10467

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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Forty-ninth Annual Meeting: Royal York Hotel, Toronto, Ontario, Canada, May 29-31, 1967.

EDITORIALS

INSTRUCTION COURSES OF THE SIXTY-SEVENTH ANNUAL MEETING OF THE AMERICAN ROENTGEN RAY SOCIETY

PRESIDENT-ELECT CLYDE A. STEVENSON requested that the Section on Instruction of the American Roentgen Ray Society continue the excellent work initiated by President-Elect, Edward L. Jenkinson, in 1939, and arrange a series of Instruction Courses also for the Sixty-seventh Annual Meeting to be held at the Hilton San Francisco Hotel, San Francisco Hotel, San Francisco, California, September 27–September 30, 1966.

This year's Instruction Courses will be given on Tuesday, Wednesday and Thursday afternoons, September 27, 28 and 29 at 3:00 P.M., and Friday afternoon, September 30, at 1:30 P.M. Each course period will be of 90 minutes' duration and no other official activity will be scheduled for this time.

A special registration desk for these courses will be set up near the general registration area. Complete information concerning the courses as well as tickets for those courses still available can be obtained Monday, September 26, from 8:30 A.M. to 4:30 P.M. and daily, Tuesday through Friday, September 27–30, 8:30 A.M. to 4:30 P.M.

Fourteen daily courses will be given on each of the first three days and ten courses on Friday; some of the courses will be given in two sessions. A complete list of the Faculty and a brief abstract for each course as well as the registration form will be found elsewhere in this issue of the JOURNAL.

Admission to all courses will be by ticket.

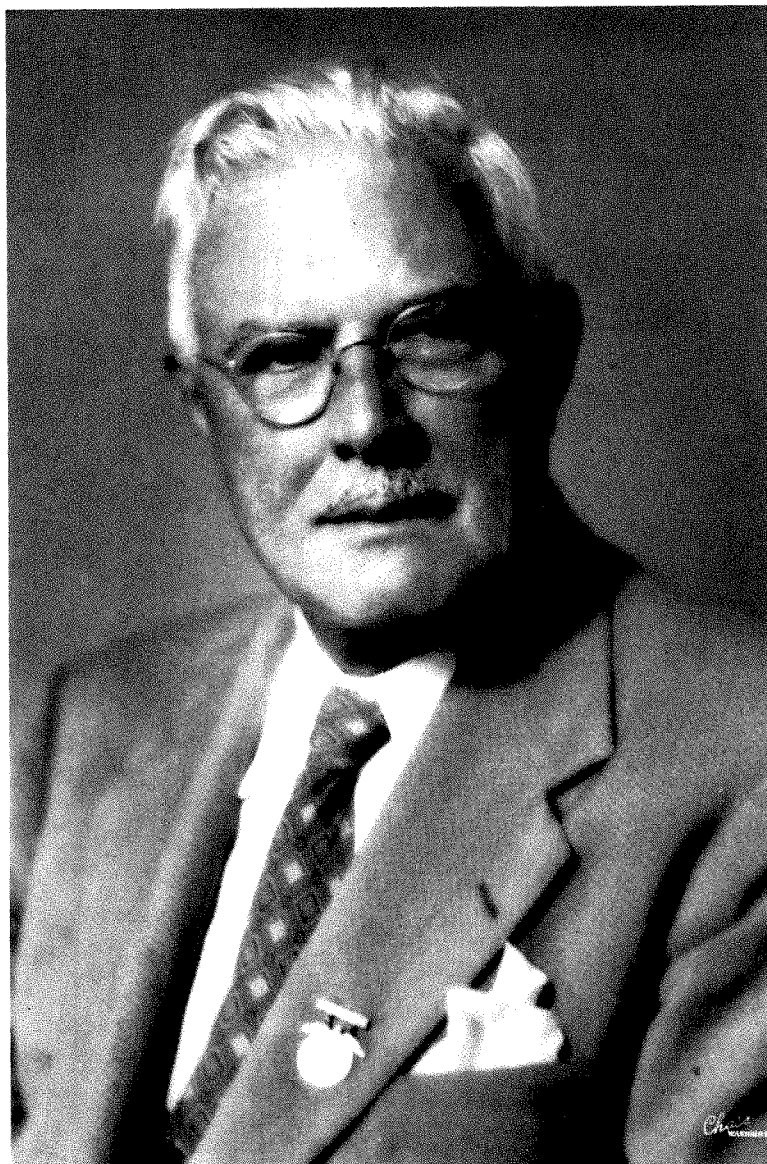
To avoid the confusion usually present on the first day of the meeting, tickets will be mailed to all those whose registration forms (pink sheets) reach the office of the Director before September 15, 1966. The envelope containing the tickets will be marked in a conspicuous manner. Please be on the lookout for your tickets and remember to bring them to the meeting. Tickets will be issued in the order that the requests are received and the *first mailing* will be shortly after September 5, 1966.

How to Register and Obtain Tickets. After reviewing the abstracts of the available courses on the following pages, fill out the pink Order Sheet. Please make three choices for each day and include the course number and name of Instructor for each choice. A \$2.00 registration fee is required from *nonmembers* for each course attended. Since it is possible to attend only one course a day for four days, the maximum fee is \$8.00. Members of the American Roentgen Ray Society, graduate students or residents in Radiology, and nonmembers who are contributing to the program, either by way of an instruction course, a paper or an exhibit, are not required to pay for these courses but must fill out the pink Order Sheet indicating their choices.

Please mail these Order Sheets to the Director of the Section on Instruction of the American Roentgen Ray Society.

HAROLD O. PETERSON, M.D.

1995 West County Road "B"
St. Paul, Minnesota 55113



URSUS V. PORTMANN

1887-1966

DR. URSUS V. PORTMANN was a big man all the way.

He was big in stature and personality; big on the football field and on the campus; big in the earlier days of that strange new field of Radiology.

He was born in Jackson, Minnesota, on January 20, 1887, the son of a physician who was born in Switzerland. He died in Tucson, Arizona, on May 21, 1966, after a lingering illness. Dr. Portmann is survived by his second wife, Mrs. Jesse Forward

Portmann; a son, Ralph, a successful businessman now in Germany; three grandchildren and two brothers, Milton C., prominent Cleveland attorney, and Arthur B., of Cincinnati.

"Port," as he was known to his intimates—and sometimes as "Ultra Violet" from his initials—was graduated from Jackson (Minnesota) High School and Adelbert College of Western Reserve University, Cleveland, where he also received his medical degree. After interning at Cleveland's St. Vincent Charity Hospital he returned to Jackson to practice for several years with his father and then joined the U. S. Army Medical Corps for active duty on December 4, 1917. After service at Camp Riley, Kansas, he was instructor and adjutant for four months at the U. S. School of Roentgenology in New York. He became a captain in MORC in June, 1918, and went to Camp Custer (Michigan) Base Hospital to mobilize for overseas duty. He was stationed at Hyres, France, in charge of the Department of Roentgenology and was discharged at Camp Sherman, Chillicothe, Ohio, on May 21, 1919. He became a major in MORC in 1929 and resigned his commission 10 years later.

He practiced in Grand Rapids, Michigan, from October, 1919, until July 1, 1922, when he joined the staff of The Cleveland Clinic Foundation, recently organized. He probably went to the Clinic because he had worked in research with Dr. George Crile, Sr., one of the Clinic founders, during his medical schools days. He was partly instrumental in inducing Dr. Otto Glasser to join the Clinic the next year, and his association with these two men probably gave the big impetus to his professional career.

Dr. Portmann was Head of the Department of Therapeutic Radiology at the Clinic and Professor of the same subject in the Clinic's Educational Institute. He became a member of The Cleveland Clinic Foundation in 1947 and held this honor until his retirement in December, 1952. Upon his retirement at the Clinic, he was hailed as "a loyal staff member." At that

time he moved to Tucson and joined the Tucson Tumor Institute. He retired from all professional activities in 1963.

At Western Reserve University, "Port" and his brother "Muff" (Milton) were great football stars. "Port" captained the famous 1908 team that beat Ohio State 18 to 0 and "Muff" captained the 1909 team. Both made the All-Ohio team and both played a few games of pro ball back in the days of Jim Thorpe and "Fats" Henry.

"Muff" still recalls a game when a player broke his leg with such a resounding crack that "Muff" went to the sidelines, sick to his stomach. "Port," though, was in his glory, putting his new medical knowledge to use, calling for splints, bandages and an ambulance. "Muff" still thinks that "Port" was one of the greatest football players he ever saw—and that covers a lot of quality.

At Western Reserve, "Port" was in the Glee Club, on the track team, made Scarsbeus, the Honorary Interfraternity Fraternity, and Nu Sigma Nu and was a member of Delta Tau Delta. In 1960, Western Reserve gave him an honorary degree of Doctor of Science.

In France, "Muff" was severely wounded and was hospitalized at Vichy. He received a telegram from brother "Port" that if he were able to be moved he should come at once to Hyres Base Hospital. If he were not, his physician brother would come to him. "Muff" packed his toothbrush and went by train in two days.

If Dr. Portmann was not in on the ground floor and of the first generation of Roentgenology, he surely was only one step up. He helped shape the present image of the American Roentgen Ray Society. In those early days, the practices of Physical Therapy and Roentgenology often were joined, and he was a member of the American Medical Association Council on Physical Therapy, Committee on Roentgen Rays. He was Secretary of its Section on Radiology for four years and became its Chairman in 1949-50.

He also was on its Committee on Radium and Medical Aspects of Atomic Energy. He

served in radiological groups from 1914 through 1952, a span of 38 years. He was a member of the Committee on Military Affairs of the American College of Radiology for five years and was an honorary member of six radiological groups in the United States, as well as of the Sociedad Columbiana de Radiología, Republic of Colombia, in 1947.

His proudest moment, however, was when in 1949 he was elected President of the American Roentgen Ray Society, which he always served with unswerving devotion and great enthusiasm. Since then, he had been a distinguished member of the Consulting Editorial Board of its official organ, the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE.

Dr. Portmann became a diplomate of the American Board of Radiology in 1934, was an examiner for it for 17 years, and a trustee from 1939 to 1956. He was on the Subcommittee on Radiology of the National Research Council for five years and Area Consultant in Radiology for the Veterans Administration from 1945 to 1952. He served as an advisory consultant in the Department of Nuclear Engineering at the University of Arizona from 1959 until his retirement in 1963.

Dr. Portmann was author or coauthor of 96 scientific papers in leading United States

and European journals and of about 150 unpublished lectures and discussions at meetings of medical societies and other groups. Many of his manuscripts were published in this JOURNAL. Among his distinguished coauthors were Dr. Crile, Sr., Dr. Glasser, Dr. Russell Haden, Dr. R. A. Hays and Dr. E. Perry McCullagh. His chief professional interests centered about the thyroid, breast cancer and dosimetry.

His greatest contribution to science undoubtedly was his work with Dr. Glasser and Valentine Seitz, Cleveland Clinic engineer, in the development, measurement and establishment of the roentgen (r) as a unit for measuring roentgen rays, and their development of the condenser r-meter for the measurement of roentgen rays and gamma rays of radium in the same unit (r and gamma r). He also compared the erythema dose with the r of the roentgen rays and gamma rays of radium in the same unit.

Dr. Portmann was big, handsome, aggressive and blunt, as are so many outstanding football players. And he also was kindly and very well-liked by both men and women who knew him. One of his Cleveland Clinic colleagues remembers him as "one of the finest men in the world."

DON DUNHAM

The Cleveland Clinic
Cleveland, Ohio 44106



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*The Faculty, Titles and Abstracts of Courses Offered
Sixty-Seventh Annual Meeting*

San Francisco Hilton Hotel, San Francisco, California

September 27 to September 30, 1966

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Harold G. Jacobson, M.D., Professor of Radiology, Albert Einstein College of Medicine; Chief of the Division of Diagnostic Radiology at Montefiore Hospital and Medical Center, New York, New York

Henry S. Kaplan, M.D., Professor and Executive Head, Department of Radiology, Stanford University School of Medicine, Palo Alto, California

Owings W. Kincaid, M.D., Section of Radiology, Mayo Clinic; Assistant Professor of Radiology, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota

Anthony F. Lalli, M.D., Assistant Professor, Department of Radiology, University of Michigan Medical Center, Ann Arbor, Michigan

Elliott C. Lasser, M.D., Chairman, Department of Radiology University of Pittsburgh, School of Medicine, Presbyterian-University Hospital, Pittsburgh, Pennsylvania

B. Peck Lau, M.D., Assistant Clinical Professor of Radiology, University of California School of Medicine, San Francisco, California

Alexander S. Macmillan, Jr., M.D., Instructor in Radiology, Harvard Medical School; Radiologist, Massachusetts Eye and Ear Infirmary; Radiologist to the Harvard Medical and Surgical Services, Boston City Hospital, Boston, Massachusetts

Richard H. Marshak, M.D., Clinical Professor of Radiology, Mt. Sinai School of Medicine, New York, New York

William Martel, M.D., Associate Professor, Department of Radiology, The University of Michigan Medical Center, Ann Arbor, Michigan

Harry Z. Mellins, M.D., Department of Radiology, State University of New York, Downstate Medical Center, Brooklyn, New York

Harvey Meyers, M.D., Associate Professor of Radiology, School of Medicine, University of Southern California, Los Angeles, California

Russell H. Morgan, M.D., Radiologist-in-Chief, The Johns Hopkins Hospital, Baltimore, Maryland

William T. Moss, M.D., Director, Department of Therapeutic Radiology, Wesley Memorial Hospital; Professor of Radiology, Northwestern University Medical School, Chicago, Illinois

Walter T. Murphy, M.D., Chief, Department of Radiation Therapy, Buffalo General Hospital; Associate Clinical Professor of Radiology, New York State University School of Medicine at Buffalo, Buffalo, New York

Sidney W. Nelson, M.D., Professor and Chairman, Department of Radiology, The Ohio State University Medical School, Columbus, Ohio

Edward B. D. Neuhauser, M.D., Professor of Radiology, Harvard Medical School; Chairman, Department of Radiology, The Children's Hospital Medical Center, Boston, Massachusetts

Charles M. Nice, Jr., M.D., Professor and Chairman, Department of Radiology, Tulane University School of Medicine; Director of Diagnostic Radiology, Charity Hospital, New Orleans, Louisiana

Gordon Potts, M.D., Assistant Professor of Radiology, College of Physicians and Surgeons, Columbia University, New York, New York

David G. Pugh, M.D., Section of Diagnostic Roentgenology, Mayo Clinic, Rochester, Minnesota

Maurice D. Sachs, M.D., Chief, Radiology Service, Veterans Administration Hospital; Associate Professor of Radiology, Western Reserve University School of Medicine; Director, Radiology Forest City Hospital, Cleveland, Ohio

Glenn E. Sheline, M.D., Professor of Radiology, University of California Medical Center, San Francisco, California

Stanley S. Siegelman, M.D., Instructor of Clinical Radiology, Albert Einstein College of Medicine;

Adjunct Attending Radiologist at Montefiore Hospital and Medical Center, New York, New York

Edward B. Singleton, M.D., Clinical Associate Professor of Radiology, Baylor University College of Medicine; Director of Radiology, St. Luke's and Texas Children's Hospital, Houston, Texas

Juan M. Taveras, M.D., Professor and Chairman, Department of Radiology, Washington University School of Medicine, St. Louis, Missouri

Jerome M. Vaeth, M.D., Director of Claire Zellerbach Saroni Tumor Institute; Clinical Associate Professor of Radiology, University of California Medical School, San Francisco, California

Don C. Weir, M.D., Clinical Professor and Acting Director of Radiology, St. Louis University School of Medicine, St. Louis, Missouri

Laurens P. White, M.D., Clinical Assistant Professor of Medicine, University of California Medical Center, San Francisco, California

Marvin M. D. Williams, Ph.D., Professor of Biophysics, Mayo Graduate School, University of Minnesota, Rochester, Minnesota

Robert E. Wise, M.D., Chairman, Department of Diagnostic Radiology, Lahey Clinic Foundation; Chairman, Department of Radiology, New England Baptist Hospital, Boston, Massachusetts

DESCRIPTION OF COURSES

COURSE 101

Tuesday

EDWARD B. SINGLETON, M.D.
Houston, Texas

Pediatric Chest Abnormalities

1. Technique
2. The normal chest and variations of normal
3. Abnormalities of the thoracic cage
4. Newborn pulmonary complications: (a) variations of perinatal distress—hyaline membrane disease, aspiration syndrome and pulmonary hemorrhage; (b) pneumonias including aspiration secondary to pharyngeal incoordination and esophageal atresia
5. Congenital anomalies: congenital lobar emphysema, congenital cystic malformation, diaphragmatic abnormalities, pulmonary agenesis and hypoplasia
6. Pulmonary abnormalities acquired in later infancy and childhood: (a) types of pneumonia and their complications; (b) acquired tracheo-esophageal fistula; (c) foreign bodies; (d) fibrocystic disease; (e) bronchiolitis

7. Rare pulmonary conditions: pulmonary alveolar microlithiasis, neoplastic diseases, pulmonary fibrosis, hemosiderosis, cytomegalic inclusion disease.

COURSE 102

Tuesday

HARRY Z. MELLINS, M.D.
Brooklyn, New York

Voiding Cystourethrography

The present status of the procedure in both children and adults will be discussed. Methods, criteria for diagnosis and limitations of the procedure will be covered. The presentation will be based upon a critical review of over 4,000 cases studied during the last 6 years.

COURSE 103 and COURSE 203

Tuesday and Wednesday

ROBERT L. EGAN, M.D.
Indianapolis, Indiana

Over Ten Years' Experience with Mammography

Course 103. Introduction and Technique of Mammography

Course 203. Diagnosis of Breast Lesions by Mammography

Over 10 years' experience has been gained with soft tissue roentgenography of the breast in a Tumor Institute with an active breast service. These studies have proved a highly accurate and valuable adjunct to the clinical and pathologic evaluation of breast lesions.

A simple and readily adaptable roentgenographic technique will be presented. Cases illustrative of typical benign and malignant disease will be shown and the diagnostic features of each described and tabulated. Differential diagnosis, sources of error, limitations of the procedure and the clinical and pathologic implications of the method will be discussed.

The results of a statistical analysis of the first 1,000 consecutive examinations (all with a follow-up from 1 to 10 years) will be reviewed. The error in 245 cases of malignant disease was 0.82 per cent.

COURSE 104

Tuesday

GIOVANNI DI CHIRO, M.D.
Bethesda, Maryland

Cisterns and Sulci in the Normal Pneumoencephalogram

The normal pneumoencephalographic anatomy of cisterns and sulci will be reviewed in detail. Particular emphasis will be placed on the "critical" areas of the endocranial subarachnoid pathways; *i.e.*, on those segments which more often are displaced or distorted in cases of intracranial space-occupying lesions. The pitfalls in the interpretation of the cisternal images and the normal variations, at the borderline with the pathologic, will be discussed at length.

COURSE 105

Tuesday

ELLIOTT C. LASSER, M.D.
Pittsburgh, Pennsylvania

Contrast Media; The Clinical Pertinence of Some Basic Physiologic and Pharmacologic Data

In the early days of the development of contrast media, the development of new products depended to a large extent upon the empirical juggling of radicals grouped about an organic ring. As basic data accumulate, however, correlating molecular structure with such factors as tissue distribution, toxicity, etc. more rational formulations of newer media should be possible. In the present course the reviewer will touch upon the following facets of this general problem:

1. The relation of molecular structure to protein binding
2. Significance of protein binding in determining excretory pathways and relative toxicities
3. Alterations in some significant enzyme systems by binding of the contrast media to the enzyme protein
4. The role, if any, that hypersensitivity may play in contrast media reactions
5. New concepts in cholecystography

COURSE 106

Tuesday

RUSSELL H. MORGAN, M.D.
Baltimore, Maryland

Screen Intensification and Cineradiography

This course will deal with the physics and technical problems associated with screen intensification and cineradiography. The discussion will consider those aspects of x-ray image formation and perception which are important in the fields of screen intensified fluoroscopy and motion picture recording. Particular

attention will be given to the practical problems associated with the use of various intensifier and cineradiographic systems in clinical radiology.

COURSE 107

Tuesday

DON C. WEIR, M.D.
St. Louis, Missouri

Roentgen Diagnosis of Injury of the Cervical Spine

The ever increasing burden of traffic on the streets and highways is resulting in an increase in the frequency of cervical spine injuries. These injuries represent acute medical emergencies and are also important in the realm of medico-legal litigation.

The atlanto-axial segment of the cervical spine is unlike the remainder of the spine both anatomically and functionally. Variations in normal alignment, dislocations, "rotation deformities," and fractures will be discussed. Reversal, or loss of the normal lordotic curve will be evaluated along with a discussion of the so-called "whiplash," the "darling" of the plaintiff's attorney and the "bane" of the defendant's attorney.

The relative value of cervical diskograms and myelograms in injury will be presented. Luschka's joints will be discussed and their clinical significance evaluated.

Technical aspects of cervical spine examinations will be outlined and evaluation of conventional views, flexion and extension, oblique studies, laminagraphy and special pillar views will be considered.

COURSE 108

Tuesday

MAURICE D. SACHS, M.D.
Cleveland, Ohio

A Practical Approach to Roentgenology of the Biliary Tract

The physiologic anatomy of the biliary tract as well as the abnormal findings will be considered in an effort to help improve diagnostic acumen.

Proper dosage will be discussed, including a plea for discontinuance of so-called "double dose" methods.

A routine technique for oral, intravenous, operative and postoperative cholangiography will be presented. The value of a fat meal, a delayed fat meal and the role of laminagraphy will be shown.

Examples of abnormal findings of the biliary tract, particularly dysfunction and fibrosis of the sphincter of Oddi, adenomyosis, pancreatitis, and carcinoma, will be presented.

COURSE 109 and COURSE 209

Tuesday and Wednesday

ALEXANDER S. MACMILLAN, JR., M.D.
Boston, Massachusetts

Sinuses and Mastoids

Course 109. Sinuses and Orbits

Course 209. Mastoids and Temporal Bone

Following a discussion of positioning, normal and some acceptable variations of the normal plus various pathologic states will be presented. As much information as possible will be given in as short a time as possible. Following the presentation, there will be opportunity for questions.

COURSE 110

Tuesday

JUAN M. TAVERAS, M.D.
St. Louis, Missouri

Extracranial and Intracranial Occlusive Vascular Disease

The discussion will include the extracranial vessels from the aortic origin and will also deal with the occlusions of main arteries and of branches of intracranial arteries.

COURSE 111 and COURSE 211

Tuesday and Wednesday

EDWARD B. D. NEUHAUSER, M.D.
Boston, Massachusetts
G. B. CLIFTON HARRIS, M.D.
Boston, Massachusetts

The New and Unusual in Pediatric Radiology

Session I. The Infant

Session II. The Child

COURSE 121

Tuesday

FRANZ BUSCHKE, M.D.
San Francisco, California

Hazards of Modern Radiation Therapy

Based on his personal experiences of over 30 years, the Instructor will discuss radiotherapeutic techniques which consistently avoid the hazards frequently considered as unavoidable in the treatment of different forms of cancer.

The discussion will include methods of avoiding clinically significant fibrotic changes of the vasculo-

connective tissue in the treatment of cancers of the pelvis and thoracic cavity, carcinoma of the bladder, and the protection of cartilage, bone, spinal cord, eye, and ear.

Statistical and casuistic demonstrations from the Instructor's material will substantiate his conclusion.

COURSE 122

Tuesday

JEROLD P. GREEN, M.D.
San Francisco, California

Radioisotopic Scanning in Clinical Diagnosis

The use and importance of scanning in clinical diagnosis of diseases in various organs of the body will be discussed. This will include brain, lung, liver, pancreas, kidney, parathyroid glands, and various tumors.

Several isotopes will be considered.

COURSE 123

Tuesday

JEROME M. VAETH, M.D.
San Francisco, California

Recent Advances in Therapy of Cancer of the Cervix Uteri

Consideration will be given to the indications and contraindications for radiation therapy of cancer of the cervix uteri. Discussion will include intracavitary and external modalities, transvaginal roentgen and cesium 137 therapy, radium and megavoltage therapy.

Clinical experimental methods, including hyperbaric oxygen, will be discussed.

Results of therapy will be given.

COURSE 201

Wednesday

WILLIAM MARTEL, M.D.
Ann Arbor, Michigan

Current Comments on Joint Diseases

A series of short presentations will be given covering the following topics:

1. *Rheumatoid Arthritis vs. Ankylosing Spondylitis.* The spine may be affected in rheumatoid arthritis and the extraspinal joints may be involved in ankylosing spondylitis but these two diseases are usually easily distinguished both clinically and radiologically.
2. *Juvenile Rheumatoid Arthritis.* Certain features differ from the adult form of the disease and the

associated growth disturbances are particularly interesting.

3. *Nontraumatic Atlantoaxial Dislocation.* The diagnostic criteria, associated diseases and clinical significance will be discussed.
4. *Rheumatoid and Psoriatic Arthritis and Reiter's Disease.* Some aspects which serve to distinguish these conditions will be considered.
5. *Gout and Pseudo-gout.* Chondrocalcinosis is not synonymous with the pseudo-gout syndrome. Hyperuricemia may be seen in pseudo-gout and chondrocalcinosis may be observed in gout as well as in other arthritic conditions.
6. *Neuropathic Joint Disease.* Some comments on the classic concept.
7. *Arthropathy Incident to Steroid Therapy.* "Charcot-like changes" have been described and avascular necrosis is known to occur.
8. *Degenerative Joint Disease.* Radiologic features and pathologic correlation.

COURSE 202

and

COURSE 302

Wednesday and Thursday

WILLIAM E. GANNON, M.D.
Brooklyn, New York

Carotid Angiography

Part I

Normal anatomy

Occlusions

(a) Internal carotid artery

(b) Intracranial arteries

Aneurysms

Arteriovenous malformations

Head trauma

(a) Subdural hematoma

(b) Epidural hematoma

(c) Internal carotid artery-cavernous sinus fistula

(d) Intracerebral hematoma and cerebral contusion

Part II

General signs of space-saving lesions

Tumors

(a) Meningiomas

(b) Gliomas

(c) Metastatic lesions

Tentorial herniation

COURSE 204

and

COURSE 304**Wednesday and Thursday****LEWIS E. ETTER, M.D.****Pittsburgh, Pennsylvania****Normal and Pathologic Roentgen Anatomy of the Skull, Paranasal Sinuses and Mastoids****Course 204**

Description of standard techniques and positions with illustrated slides for roentgen examination of the skull and paranasal sinuses. Comparison of advantages of one projection over another with respect to visibility of particular structures. General considerations with reference to the cerebral and facial components of the cranium with analysis of individual bone components that produce the various lines and shadows seen in plain roentgenograms of the skull. Examples of pathologic alterations of these normal structures will be shown. The analysis will cover studies of the sphenoid, frontal, temporal, ethmoid, parietal and occipital bones in various projections.

Course 304

Detailed roentgen anatomic analysis of the paranasal sinuses, middle ear and mastoid processes with description of precision roentgenographic techniques employed. Study of the roentgen features of the middle cranial fossa and their relations to the sphenoid and other paranasal sinuses. Consideration of the orbits and optic foramina with special attention to the frontal, ethmoid and sphenoid bone components in various projections as well as the features contributed by the zygomatic and maxillary bones.

COURSE 205

and

COURSE 305**Wednesday and Thursday****SIDNEY W. NELSON, M.D.****Columbus, Ohio****Bronchography****Course 205**

The radiologist who can properly perform and interpret bronchograms is in a position where he can make outstanding contributions to the diagnosis and understanding of many chest diseases. The proper therapy for any disease which affects the bronchial tree is often dependent upon the accurate determination of the nature and extent of the bronchial involvement. Inasmuch as the interpretation of bronchograms requires considerable knowledge of the normal anatomy of the tracheobronchial tree and some of the common anatomic variations, the pertinent anatomy will be discussed and illustrated.

A good knowledge of bronchial anatomy will enable the radiologist to systematically identify each of the major segmental bronchi, because of his knowledge of the expected distribution of each of these bronchi. The identification of each of the major segmental bronchi is extremely important in interpretation.

Once the basic bronchographic anatomy has been considered, the details of the bronchographic technique will be described. This will include the method of performing topical anesthesia, introduction of intranasal catheter, method of injecting contrast medium in order to assure systematic filling of the desired segmental bronchi, proper positioning of patient for filling of each segment, and the spot filming techniques employed to thoroughly record the filling of the desired segmental bronchi. This portion of the discussion will also include a description of some of the characteristic features of various contrast materials. The advantages of fluoroscopically controlled spot filming in comparison with conventional large film techniques will be emphasized. Good bronchographic technique can be mastered with little effort and can be quickly performed by the radiologist and his technical staff, thus precluding the necessity for resorting to the "team" approach which is often so time-consuming and frustrating in large busy hospitals.

Course 305

During the second session the majority of the different types of bronchopulmonary pathology will be discussed including the following: 1. Chronic bronchitis: a. spasm; b. excessive secretions; c. dilated mucosal glands; d. destruction of mucosa. 2. Emphysema. 3. Segmental bronchiectasis. 4. Cystic lesions. 5. Bronchogenic carcinoma. 6. Pulmonary "coin" lesions. 7. Bronchial adenoma. 8. Erosion of bronchi by adjacent calcified lymph nodes. 9. Inflammatory strictures. 10. Bronchial relocation following atelectasis of surgical removal.

The value of bronchography in the differential diagnosis of many bronchopulmonary diseases will be emphasized throughout the course, as for instance, atelectasis due to bronchogenic carcinoma or other intrabronchial lesions. Segmental bronchiectasis with associated chronic pneumonic changes may mimic neoplasms on plain chest roentgenograms, but can be clearly identified by bronchographic methods. Chronic granulomas and other infections can frequently be identified by virtue of the bronchiectatic changes produced in adjacent bronchi, thus helping to differentiate these diseases from neoplastic processes. Certain pulmonary diseases have very specific bronchographic appearances: e.g., bronchial adenomata, polycystic lung, etc.

It is hoped that this presentation will encourage radiologists to perform this extremely useful roentgenographic procedure more frequently in the future. In so doing, they will be able to make more significant contributions to the diagnosis and treatment of

the patients referred to them for study by their colleagues who are not radiologists.

COURSE 206**and****COURSE 306****Wednesday and Thursday****LEWIS S. CAREY, M.D.****St. Paul, Minnesota****Course 206. Cardiovascular Radiology—
Potpourri**

An informal presentation touching upon many aspects of cardiovascular radiology. Indications, contraindications, selection of procedure, techniques and complications of various types of cardiovascular procedures will be discussed.

Course 306. Congenital Heart Disease

This course consists of an analysis of the normal and abnormal cardiovascular silhouette. The significance of alterations in cardiovascular contour in various congenital cardiac malformations will be explained in correlative fashion by angiocardiographic studies.

COURSE 207**Wednesday****OWINGS W. KINCAID, M.D.****Rochester, Minnesota****Angiography in Renal Vascular Diseases**

The renal arteries are subject to involvement by a variety of pathologic entities, any of which may compromise renal blood flow and result in systemic hypertension. In addition to their role in the production of hypertension, these lesions are also important because many are subject to the same local complications as are similar vascular lesions elsewhere in the body.

Following a brief review of the techniques and indications for renal arteriography, the various renal artery diseases will be discussed and illustrated in detail. The use of renal arteriography following renal artery surgery will also be considered.

COURSE 208**and****COURSE 308****Wednesday and Thursday****BENJAMIN FELSON, M.D.****Cincinnati, Ohio****Course 208. The Hili and Pulmonary Vessels**

The hili and pulmonary vasculature often provide important clues in chest roentgen interpretation.

However, variations within the normal range are so broad that it often is difficult to distinguish between the normal and the abnormal. Working from a background of the normal, the course will deal with minimal changes in the roentgenogram which indicate important disease. The discussion will include the following areas: (1) hili, (2) pulmonary arteries, (3) pulmonary veins, (4) lymphatics, (5) bronchial circulation, and (6) azygos system.

Course 308. Alveolar and Interstitial Lesions in the Lung.

The problem of differential diagnosis of the vast array of disseminated pulmonary lesions is an almost insurmountable one unless specific patterns can be identified on the roentgenogram. It is often possible to recognize the diffuse alveolar pattern and, once identified, the list of its causes is relatively short. The recognition of diffuse interstitial disease is considerably more difficult, but even here it is sometimes possible to reliably distinguish this pattern and thereby reduce the etiologic possibilities to a reasonable number. In this course the roentgen features of the alveolar and interstitial patterns will be described and the various causes of each will be illustrated.

COURSE 210**and****COURSE 310****Wednesday and Thursday****J. S. DUNBAR, M.D.****Montreal, Quebec, Canada****Course 210. Pediatric Urology**

The technique of urography will be discussed, with particular emphasis on very young infants. The methods of roentgenography, the use and dosage of contrast medium, and the indications and contraindications for examination will be outlined. Particular emphasis will be placed on the diagnosis of chronic urinary tract infection and on lower tract disease. The technique of voiding cystourethrography will be discussed and illustrated by slides and cine film.

Course 310. Urinary Tract Abnormalities

Some of the normal variants which may be confused with urinary tract disease will be discussed first. Abnormalities will then be demonstrated, including upper tract and lower tract obstruction, inflammatory disease, renal trauma and new growth. Particular emphasis will again be placed on diagnosis of abnormalities in early life, since these are the problems which are least familiar to the general radiologist.

COURSE 221**Wednesday****HENRY S. KAPLAN, M.D.**
Palo Alto, California**Current Concepts in the Clinical Management of the Lymphomas**

The course will consider in detail the importance of the initial clinical work-up of the patient with lymphoma for extent of disease and the significance of staging. Factors will be discussed which guide the curative or palliative intent; the role of chemotherapy enters into this consideration.

Evidence for tumoricidal dose levels will be presented and details of planning treatment to various areas of the body will be given.

Prognostic features of the disease processes will be discussed.

COURSE 222**Wednesday****GLENN E. SHELINE, M.D.**
San Francisco, California**Radioiodine in the Diagnosis and Treatment of Thyroid Disease**

This course will include a discussion of the use of radioactive iodine in the diagnosis of functional diseases of the thyroid gland and in the treatment of thyroid cancer and hyperthyroidism.

Particular emphasis will be placed on the therapeutic aspects, with consideration of indications, contraindications, adverse effects, techniques of treatment, and results therefrom.

COURSE 223**Wednesday****LAURENS P. WHITE, M.D.**
San Francisco, California**Chemotherapy of the Whole Patient**

This course will present a point of view of the internist doing chemotherapy. It will include general considerations of various problems and emphasis on the following:

1. The secondary role of chemicals in management of lymphomas
 2. The place of drugs as an alternative to hormones in the management of breast cancer
 3. The treatment of cancers of the bowel and the ovary
 4. The use of mitomycin for carcinoma of the stomach
 5. The treatment of choriocarcinoma and leukemias
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**Course 301
and
Course 401****Thursday and Friday****RICHARD H. MARSHAK M.D.**
New York, New York**Course 301. Stomach and Duodenum**

1. Differential diagnosis of circular defects of the stomach, including submucosal tumors, polyps, metastatic lesions, etc.
2. Sarcoma of the stomach
3. Scirrhus lesions, including carcinoma, granulomatous disease, chemical strictures, etc.
4. Protein losing gastroenteropathies
5. Abnormalities in the duodenal bulb, not due to duodenal ulcer
6. Duodenitis?

Course 401. Colon

1. Inflammatory lesions of the colon (ulcerative and granulomatous colitis)
 2. Tumors of the colon, not including carcinoma
 3. Intramural hemorrhage and infarction of the colon
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**COURSE 303
and
COURSE 403****Thursday and Friday****GORDON POTTS, M.D.**
New York, New York**Course 303. Localization of Mass Lesions by Pneumography****Course 403. The Normal Carotid Angiogram**

In this course the following aspects of carotid angiography will be discussed:

1. Technique of puncturing the carotid artery
2. Selective internal and external carotid angiography
3. Some aspects of simultaneous biplane filming techniques
4. The anatomy of the vessels filled during carotid angiography

The more important anatomic variations will be described with particular reference to those which may simulate the changes caused by mass lesions. The angiographic anatomy will be related to the gross anatomy of the brain.

COURSE 307

Thursday

HAROLD G. JACOBSON, M.D.
New York, New York
STANLEY S. SIEGELMAN, M.D.
New York, New York

**The Roentgen Study of the Hand in
Systemic Disorders**

In this course the hand will be used as a pivotal structure for the demonstration of a series of abnormalities in the following categories: (1) *Congenital* (miscellaneous dystrophies, trisomy abnormalities, causes of polydactylism, etc.); (2) *some unusual manifestations of infectious diseases and granulomas* (tuberculosis, sarcoidosis, salmonella, osteomyelitis, actinomycosis, etc.); (3) *unusual residua of trauma* (thermal injuries, Sudeck's atrophy, etc.); (4) *degenerative processes* (neuropathic bone diseases of varying types, etc.); (5) *endocrine and metabolic disorders* (hyperparathyroidism, hypoparathyroidism and its variants, acromegaly, adrenal hypercorticism, maturation abnormalities, etc.); (6) *diseases of the skin and subcutaneous tissues* (scleroderma, dermatomyositis, "CRST" syndrome, Werner's syndrome, tumoral calcinosis, etc.); (7) *lympho- and myeloproliferative disorders and blood dyscrasias* (hemolytic anemias, leukemia, sickle cell dactylitis, etc.); (8) *unusual metastatic lesions*.

The pathophysiologic changes will be related to the roentgen findings in all instances.

The importance of evaluating the roentgen findings in the hands as a reflection of generalized systemic disorders will be emphasized and illustrated.

COURSE 309

Thursday

ROBERT E. WISE, M.D.
Boston, Massachusetts

**Radiographic Subtraction Technique—Video
and Color Methods**

Since the original description of photographic subtraction by Ziedses des Plantes in 1935, the method has been used sporadically. With the development of the video subtraction technique by Holman in 1963, there has been a renewed interest, especially in the field of neuroradiology. More recently, the color subtraction method has been made available and promises to be of significant value in clinical radiology as well as in teaching.

The course will deal with the techniques, advantages, and disadvantages of each of the methods available. Clinical application will be stressed.

COURSE 311

Thursday

HERMAN GROSSMAN, M.D.
New York, New York

**The Radiographic Approach to the Distended
Abdomen in the Infant and Child**

An approach to the radiographic work-up of pediatric patients (neonate to teen age) with abdominal distention will be presented. Information obtained from plain roentgenograms and the roles of special studies will be stressed.

COURSE 321

Thursday

MARVIN M. D. WILLIAMS, Ph.D.
Rochester, Minnesota

**Preparing for an Examination in
Radiological Physics**

The answers given to various types of questions in radiological physics, although not entirely incorrect, are often unsatisfactory. Frequently, the answer given is an equation, a numerical constant, or a memorized statement. The examinee frequently cannot tell (1) what conditions must be satisfied in order that the use of the equation is justified, (2) what the numerical constant represents, or (3) what the memorized statement means. This problem and some of these questions will be discussed with the aim not only of indicating a correct answer but also of showing that an acceptable answer is likely to follow naturally when the subject matter is understood. The discussion will include suggestions from other examiners in radiological physics.

COURSE 322

Thursday

WILLIAM T. MOSS, M.D.
Chicago, Illinois

**Problems in the Treatment of
Cancer of the Breast**

A discussion will be presented of the pros and cons of preoperative and postoperative irradiation. A rationale for the care of these patients will be developed and our technique of irradiation described.

COURSE 323

Thursday

B. PECK LAU, M.D.
San Francisco, California

**The Larynx—Roentgen Examination and
Therapy**

The anatomy of the larynx will be discussed. Laryngography will be reviewed with demonstra-

tions of relevant roentgenograms. A short movie will be presented.

Results in patients personally observed by the Instructor will be discussed.

COURSE 402

Friday

GEORGE JACOBSON, M.D.

Los Angeles, California

HARVEY MEYERS, M.D.

Los Angeles, California

The Acute Abdomen: Intestinal Obstruction and Other Selected Conditions

Intestinal Obstruction: A logical approach to the roentgenographic diagnosis of small and large bowel obstruction will be presented relating the roentgen features to altered physiology. The recognition of vascular impairment will be stressed.

Perforated Peptic Ulcer: The use of a water-soluble contrast medium to examine the upper gastrointestinal tract of patients suspected of having perforated peptic ulcer and the rationale for the procedure will be discussed.

Non-penetrating Injuries of the Abdomen: The discussion will pertain to the roentgen manifestations in blunt trauma to the gastrointestinal tract, liver and spleen.

COURSE 404

Friday

DAVID G. PUGH, M.D.

Rochester, Minnesota

The Diagnosis of Arthritis

The discussion will emphasize the early recognition of arthritis and the features that are important in attempting to distinguish the various types of arthritis.

COURSE 405

Friday

CHARLES M. NICE, JR., M.D.

New Orleans, Louisiana

Clinical Roentgenology of Collagen Diseases

Clinical and pathologic aspects of collagen diseases are correlated with the roentgen findings. The diseases for discussion include disseminated lupus erythematosus, polyarteritis, Wegener's granulomatosis, systemic scleroderma, dermatomyositis, and rheumatic pneumonitis.

While many of the roentgen signs in various collagen diseases are rather nonspecific, various combinations of signs or combinations of signs noted in serial roentgen studies may prove of definite diagnostic value.

COURSE 406

Friday

ANTHONY F. LALLI, M.D.

Ann Arbor, Michigan

The Tailored Urogram

The basic principles involved in executing and interpreting excretory urograms will be discussed with emphasis placed upon the tailoring of the examination to the particular problems of the individual patient. The indications for the assorted types of urograms are detailed and the methods involved are presented.

Renal and bladder neoplasms, pyelonephritis, hydronephritis, renal vein obstructions, and medullary sponge kidney disease are some of the subjects which will be covered.

Techniques such as the use of laminagraphy, nephrotomography, and percutaneous renal cyst puncture will also be included.

Problems such as renal failure dosage and reactions to contrast media and other facets of the examination will be illustrated and discussed in order to provide a guide to the best utilization of excretory urography.

COURSE 407

Friday

HAROLD G. JACOBSON, M.D.

New York, New York

Roentgen Aspects of the Structural and Other Abnormalities of the Foot

In the first half of this course, the common structural abnormalities of the foot will be described and illustrated. These will include metatarsus varus adduction deformity, club foot, the various types of pes planus, the short first metatarsal syndrome, etc.

Practical methods of diagnosing these abnormalities will be stressed and illustrated.

In the second half of the course, a number of interesting local conditions, which involve the foot, and systemic abnormalities, which are reflected in roentgen changes in the foot, will be described and illustrated. These will include: (1) *Interesting congenital abnormalities*; (2) *interesting inflammatory and granulomatous processes* (tuberculosis, sarcoid, Reiter's syndrome, etc.); (3) *various metabolic and endocrine abnormalities* (hyperparathyroidism, acromegaly, etc.); (4) *neuropathic bone disease* (diabetes, syringomyelia, leprosy); (5) *diseases of the skin and subcutaneous tissues* (scleroderma, Werner's syndrome, etc.); (6) *vascular abnormalities* (Lippman's syndrome, hemangiomas, (arteriovenous) malformations); (7) *unusual neoplasms*.

Here again, the pathophysiologic and roentgen findings will be correlated for both the local and systemic abnormalities.

Again, as in the hand, roentgen findings in the foot

will be used to illustrate various systemic manifestations.

COURSE 421**Friday****WALTER T. MURPHY, M.D.**
Buffalo, New York**Radiation Therapy of Skin Cancer**

In this course clinical results of various techniques currently used at the Roswell Park Memorial Institute for small and large lesions involving various anatomic sites, with and without invasion of cartilage and bone, will be illustrated. The discussion will accent (1) the advantages of small increment fractionation as compared to the so-called "massive-dose" technique, (2) the proper selection of radiation quality (half value layer 0.06 mm. Al, 30 kv. peak up to half value layer 0.9 mm. Cu, 200 kv. peak and radium molds) and the indications for combining dif-

ferent radiation qualities, (3) the influence of the cancer site upon the selection of field size, (4) the care of the patient during and following irradiation, and (5) the factors influencing complications and sequelae.

COURSE 422**Friday****MALCOLM A. BAGSHAW, M.D.**
Palo Alto, California**The Role of Radiotherapy in Management of
Cancer of the Urinary Bladder and of the
Prostate Gland**

The course will deal with the importance of clinical evaluation and staging of patients with cancer of the urinary bladder and of the prostate gland.

Technical considerations of treatment methods will be given with particular emphasis on megavoltage techniques.

Prognosis and results of therapy will be discussed



CONDENSED SCHEDULE OF COURSES			
TUESDAY		3:00 to 4:30 P.M.	
Diagnostic Roentgenology		Therapeutic Radiology, Nuclear Medicine, Physics and Radiobiology	
101—Singleton	Pediatric Chest Abnormalities	121—Buschke	Hazards of Modern Radiation Therapy
102—Mellins	Voiding Cystourethrography	122—Green	Radioisotopic Scanning in Clinical Diagnosis
103—Egan	Introduction and Technique of Mammography	123—Vaeth	Recent Advances in Therapy of Cancer of the Cervix Uteri
104—Di Chiro	Cisterns and Sulci in the Normal Pneumoencephalogram		
105—Lasser	Contrast Media; The Clinical Pertinence of Some Basic Physiologic and Pharmacologic Data		
106—Morgan	Screen Intensification and Cineradiography		
107—Weir	Roentgen Diagnosis of Injury of the Cervical Spine		
108—Sachs	A Practical Approach to Roentgenology of the Biliary Tract		
109—Macmillan	Sinuses and Orbits		
110—Taveras	Extracranial and Intracranial Occlusive Vascular Disease		
111—Neuhauser Harris	The Infant		

CONDENSED SCHEDULE OF COURSES**WEDNESDAY****3:00 to 4:30 P.M.****September 28, 1966**

Diagnostic Roentgenology		Therapeutic Radiology, Nuclear Medicine, Physics and Radiobiology	
201—Martel	Current Comments on Joint Diseases	221—Kaplan	Current Concepts in the Clinical Management of the Lymphomas
202—Gannon	Carotid Angiography—Part I	222—Sheline	Radioiodine in the Diagnosis and Treatment of Thyroid Disease
203—Egan	Diagnosis of Breast Lesions by Mammography	223—White	Chemotherapy of the Whole Patient
204—Etter	Normal and Pathologic Roentgen Anatomy of the Skull, Paranasal Sinuses and Mastoids—Part I		
205—Nelson	Bronchography—Part I		
206—Carey	Cardiovascular Radiology—Potpourri		
207—Kincaid	Angiography in Renal Vascular Diseases		
208—Felson	The Hili and Pulmonary Vessels		
209—Macmillan	Mastoids and Temporal Bone		
210—Dunbar	Pediatric Urology		
211—Neuhauser	The Child		

CONDENSED SCHEDULE OF COURSES			
THURSDAY		3:00 to 4:30 P.M.	September 29, 1966
Diagnostic Roentgenology		Therapeutic Radiology, Nuclear Medicine, Physics and Radiobiology	
301—Marshak	Stomach and Duodenum	321—Williams	Preparing for an Examination in Radiological Physics
302—Gannon	Carotid Angiography—Part II	322—Moss	Problems in the Treatment of Cancer of the Breast
303—Potts	Localization of Mass Lesions by Pneumography	323—Lau	The Larynx—Roentgen Examination and Therapy
304—Etter	Normal and Pathologic Roentgen Anatomy of the Skull, Paranasal Sinuses and Mastoids—Part II		
305—Nelson	Bronchography—Part II		
306—Carey	Congenital Heart Disease		
307—Jacobson, Harold Siegelman	The Roentgen Study of the Hand in Systemic Disorders		
308—Felson	Alveolar and Interstitial Lesions in the Lung		
309—Wise	Radiographic Subtraction Technique—Video and Color Methods		
310—Dunbar	Urinary Tract Abnormalities		
311—Grossman	The Radiographic Approach to the Distended Abdomen in the Infant and Child		

CONDENSED SCHEDULE OF COURSES			
FRIDAY		1:30 to 3:00 P.M.	September 30, 1966
Diagnostic Roentgenology		Therapeutic Radiology, Nuclear Medicine, Physics and Radiobiology	
401—Marshak	Colon	421—Murphy	Radiation Therapy of Skin Cancer
402—Jacobson, George Meyers	The Acute Abdomen: Intestinal Obstruction and Other Selected Conditions	422—Bagshaw	The Role of Radiotherapy in Management of Cancer of the Urinary Bladder and of the Prostate Gland
403—Potts	The Normal Carotid Angiogram		
404—Pugh	The Diagnosis of Arthritis		
405—Nice	Clinical Roentgenology of Collagen Diseases		
406—Lalli	The Tailored Urogram		
407—Jacobson, Harold	Roentgen Aspects of the Structural and Other Abnormalities of the Foot		

NEWS ITEMS

THE ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

As announced in the December, 1965 issue of the JOURNAL, the Rocky Mountain Radiological Society will hold its Twenty-eighth Midsummer Radiological Conference at the Brown Palace Hotel on Thursday, Friday and Saturday, August 18, 19 and 20, 1966.

An outstanding scientific program has been arranged. The guest speakers (in order of appearance) will be: Giulio J. D'Angio, M.D., Professor of Radiology, University of Minnesota, Minneapolis, Minnesota; Frederic N. Silverman, M.D., Professor of Radiology and Associate Professor of Pediatrics, University of Cincinnati, Cincinnati, Ohio; and Isadore Meschan, M.D., Professor of Radiology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.

Other participants will be: Mr. William C. Stronach, Executive Director, American College of Radiology, Chicago, Illinois; Jackson E. Livesay, M.D., President, American College of Radiology, Flint, Michigan; Marvin L. Daves, M.D., Denver, Colorado; Glen G. Cramer, M.D., Denver, Colorado; John W. Lane, M.D., Little Rock, Arkansas; Neal Goodman, M.D., Denver, Colorado; Andrew B. Crummy, Jr., M.D., Madison, Wisconsin; Bert Lincoln Pear, M.D., Denver, Colorado; Donald W. Brown, M.D., Denver, Colorado; and John C. Stears, M.D., Denver, Colorado.

Refresher Courses sponsored by the Radiological Society of North America will be given by Juan M. Taveras, M.D., Professor of Radiology, Washington University School of Medicine, St. Louis, Missouri.

There will be an excellent program of social activities in conjunction with the meeting.

For further information please contact

Dr. John S. Bouslog, Chairman of Publicity, 6210 East 17th Avenue, Denver, Colorado 80220.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS

At the Annual Meeting of the Association of University Radiologists, held at the University of Arkansas in Little Rock on May 13 and 14, 1966, the following officers were elected: *President*, Dr. Alexander R. Margulis, San Francisco, California; *President-Elect*, Dr. Morton M. Kligerman, New Haven, Connecticut; and *Secretary-Treasurer*, Dr. Stanley Rogoff, Rochester, New York.

The next Annual Meeting will be held at Temple University School of Medicine in Philadelphia on May 12 and 13, 1967.

POSTGRADUATE RESIDENCY IN NEURORADIOLOGY

An advanced graduate residency training program in Neuroradiology has been established within the Mayo Graduate School of Medicine and the Mayo Clinic. Applicants should be radiologists who have completed the academic requirements for certification in Diagnostic Roentgenology.

The program will provide extensive supervised training in the performance and interpretation of all neuroradiologic procedures. In addition, clinical and laboratory experience will be afforded through formal assignment to the Sections of Neurology, Neuroanatomy, Neuropathology, Neuroanesthesiology, and appropriate Research facilities. It is designed to train competent qualified teachers and investigators in the field of neuroradiology and may lead to a graduate degree (M.S. or Ph.D.) in Radiology.

For information write to C. B. Holman, M.D., Director, Training Program in Neuroradiology, Mayo Clinic, Rochester, Minnesota 55901.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

SPLENOPORTOGRAPHY: Diagnostic Phlebography for the Portal Venous System. By Lucien Leger, M.D., Professor of Clinical Surgery, Medicine Faculty of Paris; Chief Surgeon of Cochin Hospital, Paris; Member of French Academy of Surgery. Cloth. Pp. 120, with 88 figures. Price, \$8.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1965.

Dr. Leger originated the percutaneous splenic approach to splenoportography in 1951. This monograph represents his conclusions drawn from his extensive series of 2,000 cases. The text is presented in two parts. The first part is a description of technique, complications, the normal splenoportogram, and splenic manometry. The second part discusses and illustrates the splenoportographic findings in pathologic conditions, systematically arranged in sections according to the site of obstruction, the findings in splenomegalies and diseases of surrounding organs, and the study of the major abdominal syndromes. A short section on isotopic splenoportography concludes the work.

The text is profusely illustrated with roentgenograms which are, for the most part, of good quality but are presented in the customary European fashion as negatives. This does not detract from their clarity.

The illustrations are the saving grace of this book, for the text is difficult to read due to a style which does not permit easy comprehension. This difficulty is compounded by the use of phrases and terms which are unfamiliar to the American reader. In addition, the author has adopted a curious technique of referring to other work by the name of the writer without citing the reference. The lack of any bibliography seriously impairs the value of the monograph as a reference source. Much of this difficulty should have been eliminated by the American translator or editor.

With regard to technique, Dr. Leger makes no mention of the method of replacing the puncture needle with a catheter for purposes of injection, a modification which is widely accepted as a safer approach.

This monograph, though informative, is not recommended to the novice, but will be of interest to the experienced angiographer as an atlas of illustrative material.

T. E. KEATS, M.D.

BOOKS RECEIVED

CLINICAL NEURORADIOLOGY. Edited by Kurt Decker. American edition edited and translated by William H. Shehadi, M.D. Cloth. Pp. 525, with many illustrations. Price, \$45.00. McGraw-Hill Book Company, 330 West 42nd Street, New York, 1966.

PATHOLOGY OF BONE. By the late Douglas H. Collins, O.B.E., M.D., F.R.C.P., F.C.Path.; formerly Professor of Pathology, University of Sheffield; Honorary Consultant Pathologist, United Sheffield Hospitals (Royal Infirmary), and Sheffield Regional Hospital Board (Sheffield National Centre for Radiotherapy). Prepared for publication by O. G. Dodge, M.D., M.C.Path., Consultant Pathologist, Christie Hospital and Holt Radium Institute, Manchester; formerly Senior Lecturer in Pathology, University of Sheffield. Cloth. Pp. 254, with illustrations. Price, \$14.50. Butterworth Inc., 7399 Pearl Street, Washington, D. C., 1966.

DISEASES OF THE HEART. Third edition. By Charles K. Friedberg, M.D.; Cardiologist to the Mount Sinai Hospital and Attending Physician for Cardiology; Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University. Cloth. Pp., Volume 1, 1-930; Volume 2, 931-1787. Price, Single Volume, \$22.00; Two-Volume Set, \$26.00. W. B. Saunders Company, West Washington Square, Philadelphia, 1966.

GENERAL RADIATION THERAPY. By Iván Rodé, Chief Radiologist of the State Institute of Oncology, Budapest. Cloth. Pp. 550, with illustrations. Price, \$15.40. Akadémiai Kiadó, Budapest V. Alkotmány U. 21, 1966.

CURRENT DIAGNOSIS; A BIENNIAL VOLUME OF CLINICAL DIAGNOSTIC METHODS AND EVALUATIONS. Edited by Howard F. Conn, M.D., Robert J. Cloherty, M.D., and Rex B. Conn, Jr., M.D. Cloth. Pp. 843. Price, \$19.00. W. B. Saunders Company, West Washington Square, Philadelphia, 1966.

PRINCIPLES OF HEMATOLOGY. By James W. Linman, M.D., F.A.C.P.; Consultant, Section of Clinical Pathology (Hematology), Mayo Clinic; Associate Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), Rochester; formerly, Associate Professor of Medicine, Northwestern University Medical School; Chief, Hematology Section, Veterans Administration Research Hospital, Chicago. Cloth. Pp. 621, with many illustrations. Price, \$12.50. The Macmillan Company, 60 Fifth Avenue, New York, 1966.

BONE TUMOURS. By William D. Graham, M.D., F.R.C.S.(Eng.), F.R.C.S.(Edin.), F.R.C.S.(G), F.A.C.S., Professor of Orthopaedic Surgery, Univer-

sity of Witwatersrand, Johannesburg; Chief Orthopaedic Surgeon, Johannesburg General Hospital Group; Chairman, Bone Tumour Registry (South Africa). Cloth. Pp. 144, with illustrations. Price, \$10.50. Butterworth Inc., 7300 Pearl Street, Washington, D. C., 1966.

VIRUSES OF LABORATORY RODENTS. National Cancer Institute Monograph 20. February, 1966. Edited by Robert Holdenried. Cloth. Pp. 180, with many tables and few illustrations. Price, \$2.50. U. S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, Bethesda, Maryland. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., 1966.



ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

GROS, CH., WALTER, J. P., GIRARDIE, J., and SCHMELTZER, A. Écoulements mamelonnaires lactoïdes et endostose crânienne. (Milk-like discharges from the nipple and cranial endostosis.) *J. de radiol., d'électrol. et de méd. nucléaire*, Dec., 1965, 46, 827-834. (From : Chaire d'Électroradiologie, Service Central du C. H. U., Strasbourg, France.)

A series of 122 cases of discharge from the nipple was collected, excluding cases of malignant disease. Of these, 36, or 29.5 per cent, presented cranial endostoses, as compared to only 11.2 per cent in a control group of 250 women.

It has long been known that these endostoses relate to syndromes of 2 kinds: (1) endocrine and metabolic (obesity, virilism, glycemic regulation, tetany, calcific disorders); and (2) neuropsychic taints (cephalgias and character, affective or intellectual factors). The discovery that there also is a significant correlation with breast disorders indicates that there is a common ground on which they rest.

The 36 cases were evaluated radiologically as to the type of cranial disorders; the breasts were studied with plain roentgenograms and the ducts visualized by means of contrast injections. All but 4 showed mammary pathology as follows: 14 with hyperplasia, 7 with fibro-cystic dysplasia, 6 with simple canal ectasia, 3 had adenomas, there was 1 mastopathy of menopause, and 1 had a benign dendritic tumor. One-third of this group had had no children; of the 25 who had, only 14 had nursed them, and but for an average of 4 months.

Since the breast is the organ of giving—the emblem of woman, wife and mother, it creates psychologic problems which are not studied with the same detail as that accorded to women with ulcer, colitis or asthma. The breast is an accessory factor influencing moral, conjugal and social life. Culpability, anguish, frigidity and conflicts may relate to psychosomatic disorders when there are mammary disharmonies. These women are apt to develop nervousness, worries and depression, leading to marital conflicts. Therefore, they should be investigated not only physically, but psychologically and radiologically as well.—*Frank A. Riebel, M.D.*

GONZALEZ, LUIS L., and LEWIS, CARSON M. Cerebral hemorrhage following successful endarterectomy of the internal carotid artery. *Surg., Gynec. & Obst.*, April, 1966, 122, 773-777. (From: Department of Surgery, Veterans Administration Hospital, and University of Cincinnati College of Medicine, Cincinnati, Ohio.)

Successful endarterectomy of the internal carotid artery has been followed in the authors' and other

investigators' experience by a significant occurrence of ipsilateral hemorrhagic infarction.

The authors report a series of 3 adult patients presenting with clinical findings compatible with acute occlusion of one internal carotid artery. The patients were evaluated shortly after hospitalization by arteriography. These studies revealed arteriosclerotic disease of the carotid and/or vertebral systems associated with complete occlusion of one internal carotid artery. Endarterectomy followed within 2 to 6 days. Shortly after the restoration of circulation, symptoms of severe neurologic deficit developed. The patients expired from 1 to 16 days after surgery. Histologic confirmation of cerebral infarction was obtained in 2 patients, and grossly bloody cerebral spinal fluid was felt to support this clinical impression in the third.

The authors, adding their experience to a limited number of cases reported by other investigators, conclude that this complication may follow successful endarterectomy in a significant number of cases, perhaps as high as 50 per cent.

Clinical and experimental evidence relative to this problem indicates that the ischemia secondary to internal artery occlusion produces endothelial damage which, after successful restoration of blood flow, may result in hemorrhagic infarction.—*Frederick R. Cushing, M. D.*

ROBINSON, H. S. Rheumatoid arthritis—atlanto-axial subluxation and its clinical presentation. *Canad. M. A. J.*, Mar. 5, 1966, 94, 470-477. (Address: Medical Director, Canadian Arthritis and Rheumatism Society, B. C. Division, 900 West 27th Avenue, Vancouver, British Columbia, Canada.)

Atlanto-axial subluxation is relatively common in rheumatoid arthritis. A table summarizes the findings in 22 patients with odontoid-atlas separation. They were relatively severe cases, and 50 per cent had rheumatoid nodules and the majority had positive rheumatoid factor tests and elevated serum gamma globulin. The arthritis had been present 7-34 years. It was usually impossible to determine the duration of the subluxation.

Fourteen of 22 patients had symptoms or clinical findings suggesting subluxation but the other 8 had no positive findings or complaints. Headache was usually occipital. Two patients had temporary quadriplegia. Others complained of weakness of the arms or neck, vertigo or paresthesia. Three patients had objective evidence of cord compression.

Physical examination showed the spine at C2 to be prominent on forward flexion. A lateral roentgenogram in forward flexion demonstrated the subluxation to best advantage; neutral position failed to show the lesion in 7 patients. Erosion of the odontoid was noted in several of the severe cases associated with local erosions of arches or facets.

Conservative therapy is recommended except in patients with acute cord compression or damage, or severe pain.

Four case histories are included.—*Martha Mottram, M.D.*

NECK AND CHEST

SHAUFFER, IRVING A., and COLLINS, WALTER F.

The deep clavicular rhomboid fossa: clinical significance and incidence in 10,000 routine chest photofluorograms. *J.A.M.A.*, Feb. 28, 1966, 195, 778-779. (Address: Dr. Shauffer, 1722 Beacon Street, Brookline, Mass.)

The rhomboid fossa consists of a roughened area along the lower surface of the medial end of the clavicle which serves as an attachment for the costoclavicular ligament that binds the clavicle to the first rib. In some persons the fossa is exaggerated so that the appearance is a crescentic defect which is delineated from the remainder of the clavicle by a band of increased density.

Because of widely varying figures in the literature regarding the frequency of occurrence of the condition, the authors reviewed 10,000 chest photofluorograms made at the Boston City Hospital outpatient department. Very shallow rhomboid fossae are not unusual findings, and only those fossae were tabulated which were notched in appearance and were delineated from the rest of the clavicle by a distinct band of density. Fifty-nine cases were found, an incidence of 0.59 per cent. Thirty-nine were unilateral, 30 being on the right and 9 on the left; 20 were bilateral. Only 5 of the 59 patients were females.

Three cases in which deep rhomboid fossae were demonstrable are reported in detail; all were males.

The authors feel that review of the subject and presentation of the cases would call attention to this anomaly and emphasize its lack of pathologic significance, thus discouraging further investigation which might prove costly or even harmful to the patient.—*James R. Knapp, M.D.*

GAENSLER, EDWARD A., GOFF, ANNE M., and PROWSE, CLIVE M. Desquamative interstitial pneumonia. *New England J. Med.*, Jan. 20, 1966, 274, 113-128. (From: Thoracic Services, University Hospital, and Departments of Medicine and Surgery, Boston University School of Medicine, Boston, Mass.)

The clinical, roentgenologic, pathologic and pathophysiologic features in 12 patients with desquamative interstitial pneumonia are described. This is a chronic interstitial pneumonia which roentgenographically presents with slight triangular haziness radiating from the hili along the heart borders to both bases but sparing the costophrenic angles. Increase in the number and thickness of the basal vas-

cular markings, with loss of definition, is also characteristic. In some cases there is a progressive loss of volume of the lower lobes. Complications include pleural effusion and spontaneous pneumothorax.

Clinically, the chief complaint is dyspnea. Occasionally clubbing and exertional cyanosis are present.

Long term follow-up in 5 patients suggests that the course of the disease may be more benign and the outlook better than in the more usual forms of idiopathic chronic interstitial fibrosis. Dramatic subjective and objective improvement within a few days after the onset of treatment with corticosteroids in 4 cases indicates that these patients respond more favorably to steroids than those with other chronic interstitial pneumonias.

The histologic picture is characterized by desquamation of masses of large alveolar cells into the distal air spaces. The pleura as well as arterial walls are often thickened.

Physiologic studies reveal hyperventilation, a marked increase of alveolar arterial oxygen gradient and slight oxygen unsaturation due to venous admixture.

The authors believe that this entity is distinct from other chronic interstitial pneumonias such as the Hamman-Rich disease.—*Francis P. Shea, M.D.*

STRELLING, M. K., RHANEY, K., SIMMONS, D. A. R., and THOMSON, J. Fatal acute pulmonary aspergillosis in two children of one family. *Arch. Dis. Childhood*, Feb., 1966, 41, 34-43. (From: Royal Infirmary, Dundee, and Departments of Child Health and Bacteriology, Queen's College, University of St. Andrews, Dundee, Scotland.)

The authors report 2 children with fatal pulmonary aspergillosis, both of whom had previously been normal in health. Usually diffuse pulmonary infection with aspergillus has developed as a complication of a pre-existing disorder. In general, invasive pulmonary aspergillosis is uncommon in man and is rare as a cause of death in children.

In these 2 children there was a history of established contact with a contaminated environment. The histologic appearances and the demonstration of the fungus definitely support the presence of infection with *Aspergillus fumigatus* which caused their demise.

The most common manifestation of pulmonary aspergillosis is the formation of a localized filamentous network, or aspergilloma, within bronchi, lung cavities or areas of devitalized lung tissue, without evidence of invasion of surrounding cellular structures. Although this may cause mild episodes of hemoptysis, symptoms are few and the fungus is generally regarded as having a saprophytic relationship with the host. However, aspergillus may eventually infect the bronchi, spreading over the bronchial mucosa without penetrating it and may give rise to symptoms associated with hypersensitivity. The

least common manifestation is pulmonary invasion by the fungus which has usually been reported in the presence of pre-existing lung disease, severe metabolic disturbance or a generalized disorder, particularly one involving the lymphoreticular system.

The authors review the reported cases of invasive pulmonary infection from aspergillus in children. In infancy this condition may be a fulminating one with death in a single week. In fact, none of the children with the acute form have survived for more than 4 weeks. The infection has been unaffected by a wide range of antibacterial therapy. Dissemination outside the lungs may occur and may give rise to pustulous skin lesions, hepatomegaly or meningitis. Moreover, a fungal endocarditis has been reported in generalized aspergillosis.

The roentgenologic picture is one of a diffuse, fine or coarse, fluffy-edged mottling of the lung fields. However, the appearances are not specific for aspergillosis and may be seen in invasive pulmonary disease due to other fungi, pulmonary tuberculosis or in other lung diseases.

At the pathologic examination widespread pale nodular lesions in the lungs have been found and within these the fungus has been demonstrated. It is considered extremely difficult to obtain confirmation by means of positive cultures from patients during life.

This disease should be thought of in the differential diagnosis of puzzling acute pneumonic illnesses, particularly when they accompany roentgenologic findings of diffuse mottling of the lungs and neutrophil leukocytosis. The entities that may produce a similar roentgenologic appearance but less acute clinical illness are such rare disorders as *Pneumocystis Carinii* pneumonia, pulmonary alveolar proteinosis, acute interstitial pulmonary fibrosis and acute beryllium pneumonitis.—*Lionel W. Young, M.D.*

CLAUS, E., and DOCHEZ, CH. Miliaries lipiodolées pulmonaires: complications de l'hystéro-salpingographie et d'accidents vasculaires. (Miliary lipiodol emboli: complications of hystero-salpingography and vascular accidents.) *J. belge de radiol.*, 1966, 49, 18-24. (Address: Dr. E. Claus, Medisch Centrum, St-Jacobsmarkt 49, Antwerpen, Holland.)

Three cases are reported in which lipiodol caused miliary pulmonary opacities. In one, a roentgenogram of the chest made to investigate a cough revealed many opacities of metallic density; the patient then acknowledged that 10 days before she had had a hystero-salpingography, with prompt development of pain, malaise and cough. In the second case, the radiologist observed the intravasation of oil fluoroscopically during hystero-salpingography, while in the third, pulmonary emboli resulted from an erroneous intravenous injection of 10 cc. of the opaque medium. All patients recovered.

To investigate the problem further, the authors injected lipiodol into ear veins of 5 rabbits. The first animal died during the injection of 5 cc.; another died from slow injection of 3 cc.; a third died from rapid injection of 1 cc.; and the remaining 2 lived, after injections of 1 cc. and 3 cc. respectively.

The authors recommend that hystero-salpingography be performed only by qualified gynecologists; that rubber cannulas and water-soluble opaque media be used; and that the procedure be carried out under fluoroscopic control.—*Frank A. Riebel, M.D.*

BAKER, R. ROBINSON, and WAGNER, HENRY N., JR. Pulmonary embolectomy in the treatment of massive pulmonary embolism. *Surg., Gynec. & Obst.*, March, 1966, 122, 513-516. (From: Departments of Surgery, Medicine, and Radiology, The Johns Hopkins University School of Medicine, Baltimore, Md.)

The first successful pulmonary embolectomy, under cardiopulmonary bypass, was performed by Sharp in 1961. Two years later, a further report by Baker described the clinical management of 4 additional patients.

The authors summarize their experience gained in the treatment of 9 more patients, and the current criteria for performing pulmonary embolectomy in the management of the disease. The entire series consisted of 13 patients who had emboli of sufficient size to occlude either the entire right or left main pulmonary artery. This occlusion was documented by pulmonary scanning, arteriography, operation, or autopsy. Hypotension was present in 8 patients, none of whom survived the massive embolism. A definite diagnosis was made in all 5 patients in whom pulmonary arteriography or pulmonary scanning had been carried out. Blanching of the pulmonary vasculature as described by Torrance was present in 7 of 12 of the roentgenograms of the chest. A characteristic electrocardiographic finding was present in only 5 of the 13 patients.

On the basis of their united experience, the authors feel that the indications for emergency embolectomy are: (1) evidence of pulmonary embolism by history and physical examination; (2) hypotension; (3) right ventricular failure; (4) blanching of the pulmonary vasculature of one or both lung fields on the roentgenograms of the chest; and (5) characteristic electrocardiograms.

Hypotension may be the most important indication for emergency embolectomy. Pulmonary scanning provides an accurate test which can be performed quickly and without hazard to the patient, particularly as a screening procedure. If this is indicative of major embolism, arteriography is also indicated when the patient's clinical condition permits and surgery is contemplated. Although more time-consuming and hazardous, the method does provide a more accurate account of the status of the larger

arteries. Bedside cardiac catheterization with localization of the catheter tip by electrocardiographic tracing is a diagnostic test described by Guercio and associates and may provide important evidence for emergency operation. In the absence of pulmonary edema or mitral valvular disease, they found that patients with a mean right ventricular pressure of less than 30 cm. of saline survived, while those with a greater pressure died. The authors feel that this technique warrants further investigation.

Spontaneous return of pulmonary blood flow has been documented by means of serial scanning in 2 patients with massive embolism. The blood flow to the right lung was almost completely absent, but without associated hypotension, and both patients survived following vena caval plication and heparin therapy. This observation indicates that it is necessary to take extreme caution in deciding to perform an embolectomy. Vena caval plication or ligation may be the preferred procedure in many instances.—*James R. Knapp, M.D.*

TIMMIS, GERALD C., GORDON, SEYMOUR, and REED, JOSEPH O. Spontaneous closure of an atrial septal defect. *J.A.M.A.*, April 4, 1966, 196, 17-19. (Address: Dr. Timmis, 5224 St. Antoine Street, Detroit, Mich.)

The authors present, to the best of their knowledge, the first reported case of spontaneous closure of an atrial septal defect, noting, however, that this observation has been made by others.

The patient, a 3 year 9 month old boy, was first admitted to Children's Hospital of Michigan at 6 months of age with a diagnosis of right upper lobe bronchopneumonia. The initial chest roentgenogram revealed the pneumonia, pulmonary hypervascularity, and cardiomegaly. The electrocardiogram was compatible with subepicardial damage. Following therapy the patient was discharged with the diagnoses of bronchopneumonia, congestive heart failure and myocarditis.

The patient was re-admitted at 8 months of age for cardiac evaluation. Cardiac catheterization and selective angiocardiography revealed evidence of a left to right shunt at the atrial level. A second catheterization and angiocardiography reconfirmed this diagnosis.

Following an asymptomatic period of 2 years, the patient was readmitted for further cardiac appraisal. At this time, the chest roentgenogram revealed residual cardiomegaly. The electrocardiogram demonstrated a shift to a more neutral axis from the previous right deviation. Repeat cardiac catheterization and angiocardiography revealed spontaneous closure of the atrial septal defect.

Explanations for the more common spontaneous closure of ventricular septal defects are not applicable to this phenomenon. In view of both clinical and electrocardiographic evidence, myocarditis, involving

the atrial septal wall may have been responsible for sufficient tissue reaction to effect spontaneous closure of this defect.—*Frederick R. Cushing, M.D.*

GENERAL

LINDQUIST, J. M., PLOTKIN, S. A., SHAW, L., GILDEN, R. V., and WILLIAMS, M. L. Congenital rubella syndrome as a systemic infection: studies of affected infants born in Philadelphia, U.S.A. *Brit. M. J.*, Dec. 11, 1965, 2, 1401-1406. (Address: Dr. Lindquist, Department of Pediatrics, Philadelphia General Hospital, Philadelphia, Pa.)

Affected infants born 6-9 months after an epidemic of rubella in Philadelphia, Pennsylvania, were studied as to epidemiology, clinical manifestations, and serologic findings. During a 12 month period, including the epidemic and these births, there was a substantial increase in congenital defects consisting of osseous lesions, hepatosplenomegaly, anemia, and deficiency of megakaryocytes in the bone marrow as well as retardation of intrauterine growth, neonatal thrombocytopenia purpura, and cataract formation. A control 12 month period revealed 0.31 per cent of such abnormalities, while the period under discussion showed 1.0 per cent of such abnormalities.

Forty infants were born with these abnormalities, 20 of whom had viral isolation or a history of maternal rubella. Rubella virus was isolated from 68 per cent of infants with probable rubella syndrome. Congenital heart disease was present in 75 per cent of rubella syndrome suspects. Seven had patent ductus arteriosus, 4 of which were necessarily ligated, 2 with associated coarctation of the pulmonary artery branches, and 1 with a ventricular septal defect. Ventricular septal defect was also found in 4 other cases, 1 of which had pulmonary artery branch coarctation.

Two infants exhibited endocardial cushion defects and 1 other infant had pulmonary stenosis. Cataracts were seen, either at birth or developing within a few weeks of birth in 60 per cent of the infants. Fifty per cent of these rubella syndrome patients were small at birth (under 2,500 gm.). Bone abnormalities were present in 10 or 50 per cent of the rubella syndrome infants, consisting of irregular mineralization of the metaphysis of the long bones, principally the shoulders and knees. There were radiolucent transverse zones and longitudinal bands of demineralization alternating with normally dense areas. Irregular zones of provisional calcification were present in the femora, the pelvis, and tarsal ossification centers. Serial bone roentgenograms revealed resolution of these abnormalities in 5-8 weeks in all but 1 infant who had retained them to 5 months of age.

The authors explain the bone changes on the basis of viral osteitis based on increased osteoclasts during the abnormal phase and an increase in osteoblasts in

the reproductive phase. The 1 infant with persistent defect showed no osteoblastic increase.

Rubella virus has been isolated from the bone marrow by Zerkhorn and Medians.

The epidemiologic potentialities of these virus-excreting infants are mentioned and discussed.—*Sam Campbell, M.D.*

RADIATION THERAPY

SANTIAGO, ARTURO. An intraoral stent for the direction of radiation beam therapy. *J. Pros. Den.*, Sept.-Oct., 1965, 15, 938-944. (From: University of Puerto Rico School of Dentistry, San Juan, Puerto Rico.)

Radiation injury in normal tissues increases directly in proportion to the volume of tissue that is irradiated. Normal tissues must be included in the beam to ensure an adequate margin around the lesion, but excessive size of the field should be avoided. The intraoral stent, an acrylic resin device designed and made for the individual patient, provides direction and fixation of the radiation beam and thus reduces unnecessary radiation to normal tissues.

The author discusses treatment planning for a case with lower gingival squamous cell carcinoma. Steps and methods of making such a stent are illustrated.

The results were excellent, with very minimal amount of radiation reaction in the surrounding normal tissue.—*Surendra K. Bansal, M.D.*

SANTIAGO, ARTURO. Use of intra-oral prostheses in radiotherapy. *M. Rec. & Ann.*, Jan., 1965, 58, 3-11. (From: University of Puerto Rico School of Dentistry, San Juan, Puerto Rico.)

The use of intraoral prostheses is very helpful in avoiding complications due to unnecessary radiation to normal tissues of the oral cavity while treating malignant disease.

The author discusses the role of the dentist in making such prostheses.

Five different kinds of these appliances are presented, and these are:

- (1) Prostheses to displace the tongue to either side, upward or downward, and posteriorly.
- (2) Prostheses for radiation beam direction.
- (3) Prostheses used as a radium carrier.
- (4) Prostheses used in measuring radiation.
- (5) Prostheses used as tongue protector.

All these prostheses can be made easily by the instruments and materials used in the dental office and dental laboratory.—*Surendra K. Bansal, M.D.*

MALEKI, A., HASHEMIAN, H., and AFCHARI, R. Le cancer de l'oesophage en Iran. (Esophageal cancer in Iran.) *J. de radiol., d'électrol. et de méd. nucléaire*, March-April, 1965, 46, 135-142. (From: Centre anticancéreux

de Téhéran: Service de Radiologie et Service de Chirurgie, Teheran, Iran.)

This study is based on 450 cases observed during 4 consecutive years at the Teheran Anticancer Center and in the private office of one of the co-authors. Cases of adenocarcinoma of the cardia were excluded from the statistics.

Two facts are striking: the high number of female patients (165) and the imposing proportion of young subjects (82 cases were below 40 years of age).

The lower third of the thoracic esophagus is the area most frequently involved (48 per cent).

The histologic diagnosis proved to be squamous cell carcinoma in all the cases, with 2 exceptions: 1 epithelio-sarcoma and 1 pure sarcoma.

Dysphagia was the usual symptom noted clinically.

The classic treatment consisted of surgery or radiotherapy or their combination. As a principle, radiotherapy alone was the treatment for the cervical esophagus, surgery for the cardia and surgery or radiotherapy or their combination for the thoracic localization.

Surgical technique. Surgical removal of the lesion was followed by esophago-gastric anastomosis. In the cases where severe stenosis was judged non-resectable, a funnel tube (Mousseau-Barbin) was inserted to by-pass the obstruction and to feed the patient. This technique was preferred to simple gastrostomy. Among the 450 cases, 100 were subjected to esophagectomy and one-third of these died in the following 48 hours. This high mortality rate is explained by the poor general condition of the patients and the always advanced stage of the lesion.

Radiotherapy technique. Following the routine examinations, radiographs to ascertain the exact location of the lesion are taken with the aid of transverse axial tomography and lateral exposure with the cobalt 60 unit in the position of treatment and using lead markings on the skin. Bronchoscopy is regularly performed if the lesion is close to the hilar area, although the authors rely more on the information contained in the lateral roentgenogram than on endoscopy. Of course, lesions showing a fistula formation or being on the verge of fistulating are not irradiated; however, the shaggy margins of a lesion are not a contraindication, although they call for a careful treatment and radiographic control during the course of treatment.

After the tracing of the isodose curves, 4 fields are used to deliver a tumor dose of 7,000 to 7,500 r in 6 to 7 weeks. During the last year, an electrocardiographic study was made when 5,000 r had been given and if there was any alteration. the seances were spaced further apart and the left anterior field was omitted.

Complete statistical results cannot be given due to the difficulties in obtaining a thorough follow-up. Surgical treatment did not appear to be superior to

cobalt 60 therapy. For the whole group, 7 per cent are still alive 1 year after the initial treatment.—*H. P. Lévesque, M.D.*

HALNAN, KEITH E. The place of non-surgical methods in diagnosis and management, and the long-term value of treatment of thyroid cancer. *Brit. J. Surg.*, Oct., 1965, 52, 736-739. (From: Christie Hospital and Holt Radium Institute, Manchester, England.)

The incidence of thyroid cancer is low, perhaps 12 cases per million population per year. Diagnosis should be made as early as possible, and by biopsy or thyroidectomy for any unexplained, new or growing nodule. One very important aid in diagnosis is the radioiodine scan. A malignant nodule rarely, if ever, concentrates more radioiodine than the normal thyroid gland, and will usually show up as an inactive or "cold" area.

Diagnostic radiology is of some use. Compression or deviation of the trachea is uncommon from non-thyroid tumors; the psammoma bodies of papillary carcinoma can sometimes be seen by using great care; and calcification of the lymph nodes makes metastases an unlikely diagnosis. Metastases in lymph nodes, bone, or lung may be the first evidence of thyroid cancer. The accuracy of diagnosis is not high, about two-thirds of the cases being recognized preoperatively; in the remaining one-third unfortunately it is the pathologist who produces the correct answer, often most unexpectedly.

The papillary adenocarcinomas commonly metastasize to lymph nodes, grow very slowly, and are of excellent prognosis. The follicular adenocarcinomas may spread by blood-stream to bone or lung; therefore, have a less favorable prognosis but nevertheless grow slowly and may be successfully treated. The anaplastic growths, usually occurring in the older age groups, invade locally, by lymphatics and by blood-stream, leading to death rapidly by one of these three ways. Atypical tumors of the thyroid include Hürthle-cell tumors (which may be benign or malignant), squamous cell carcinoma (which has the unpleasant features of other anaplastic growths), and reticulosarcoma (which is radiosensitive but usually recurs early).

The four modalities of treatment are surgery, irradiation, radioiodine therapy and hormone administration. Although surgical excision, *when complete*, is obviously the best method, total thyroidectomy is needed in many cases, and local recurrence, often after many years, is not uncommon. It is exceptional for there to be no uptake of radioiodine postoperatively after total thyroidectomy. Roentgen irradiation has been improved in the last 10 years by the wider use of megavoltage, which gives better depth doses, avoids undesirable high dose to skin and bone, and especially makes it easier to give homogeneous exposure to the desired volume while

avoiding undesirable areas, such as the spinal cord. Compared with radioiodine therapy, this form of treatment has the advantages of better control of the radiation dose given. The main place for roentgen irradiation alone is for the treatment of undifferentiated tumors, some of which may be cured, and a temporary remission achieved in most. One must also remember the great value of palliative roentgen irradiation in relieving unpleasant symptoms from isolated metastases, especially painful bone metastases.

The obvious use for radioiodine therapy is in inoperable well-differentiated tumors, especially with metastases. Since radioiodine therapy is limited by the concentrating power of the tumor cells, this needs to be increased by preliminary ablation of normal thyroid tissue which gives rise to increased endogenous thyroid stimulating hormone (TSH), and, if need be, by injections of exogenous TSH. Hormone treatment (thyroxine) is now of established value in a few patients with well-differentiated tumors, but it is impossible to predict which tumors will be thyrotropin-dependent, or for how long they will respond to treatment. Hypophysectomy has been tried in a few patients without success so far. Steroid treatment and chemotherapy are both worth more trial after all other methods have failed.

The fact to be emphasized is that no one treatment will usually be adequate alone. Combined treatment should be given wherever possible, and preferably at the first opportunity. Thyroidectomy for operable cancers of any kind should be followed both by radioiodine therapy and by thyroxine administration. Inoperable, well-differentiated (potentially functioning) cancers should be treated with radioiodine, the main (second) dose of radioiodine being followed by both roentgen irradiation and thyroxine administrations. Inoperable, undifferentiated (non-functioning) tumors can only be treated by roentgen therapy.

The 10 year survival figures for over 300 patients are reported. The main points are that a substantial proportion even of the patients with operable (Stage 1) tumors dies by 10 years, but that a small proportion even of the very advanced cases (Stages 3 and 4) could be usefully treated over 10 years. These results also demonstrate the well-known great difference between the prognosis of patients with well and poorly differentiated cancers. Another finding of note is that in 268 deaths from thyroid cancer in which there was some knowledge of the circumstances, the primary tumor was implicated in about 30 per cent, presumably causing respiratory obstruction in most.

One may be able to improve on these poor results just as much from early diagnosis and operation as from improving management after diagnosis. There is a clear relationship between age at diagnosis and survival; the younger the patient, the better the prognosis.—*Edwin LePar, M.D.*

STEHLIN, JOHN S., JR., SMITH, J. LESLIE, JR., JING, BAO-SHAN, and SHERRIN, DARRELL. Melanomas of the extremities complicated by in-transit metastases. *Surg., Gynec. & Obst.*, Jan., 1966, 122, 3-14. (From: Departments of Surgery, Pathology, and Radiology, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.)

"In-transit metastases" are a unique feature of malignant melanomas arising on the extremities. They are described as cutaneous or subcutaneous metastases which may occur anywhere between the primary lesion and the regional lymph nodes. The term of satellitosis is used for definite intracutaneous melanomas which appear within the immediate vicinity of the primary lesion.

Superficial in-transit metastases present as one or more visible or palpable, painless lesions in the skin or subcutaneous fat. They may be pigmented and are usually 1-2 mm. in diameter. Deeper lesions appear as painless, nontender nodules. There may be edema of the extremity. Coalescence of the deposits into large masses may be associated with pain, ulceration, and hemorrhage. Microscopically, lymphatic channels are seen to be dilated and obstructed.

Lymphatic obstruction is considered as the principal contributing factor although the exact pathogenesis is unknown. Melanoma cells are thought to metastasize in the form of emboli from the primary lesion to the regional lymph nodes.

The ratio of upper to lower extremity involvement in this series of 70 patients was 15/55. In 50 per cent of the patients there was involvement of the skin and subcutaneous tissues. This was associated with a 50 per cent incidence of regional lymph node metastases. One-third of the patients had only subcutaneous involvement with a 75 per cent incidence of regional lymph node metastases. The remainder of the group had intracutaneous involvement and a 20 per cent incidence of positive regional lymph nodes.

The presence of in-transit metastases carries a grave prognosis. Sixty per cent of patients who had positive regional lymph nodes and subsequently developed in-transit metastases were dead within 1 year. Only 19 per cent were living after 2 years and the projected 5 year survival rate of this group was 8.7 per cent. Comparable figures for patients with negative lymph nodes are an 8 per cent mortality for the first year with 67 per cent living after 2 years and a projected 5 year survival rate of 18.7 per cent.

Treatment was considered most effective in a group of 36/70 patients who were perfused with or without excision of the metastases as compared with a group of 21/70 treated by surgical procedures alone and 13 patients who were not treated surgically.—*Henry Haven, M.D.*

SHAPIRO, SAM, STRAX, PHILIP, and VENET, LOUIS. Evaluation of periodic breast cancer screening with mammography: methodology and early observations. *J.A.M.A.*, Feb. 28, 1966, 195, 731-738. (Address: Mr. Shapiro, 625 Madison Avenue, New York, N. Y.)

This is a preliminary report of a breast cancer screening program begun in December, 1963, for females enrolled in the Health Insurance Plan of Greater New York utilizing both clinical examination and mammography.

There are to be 30,000 women between 40 and 64 years of age in each of two groups, one of which receives two annual follow-up examinations after an initial examination, the other of which receives no special attention as far as the breast is concerned. Routine mammograms are made in two projections using the Egan technique.

Thus far, 9,883 women in the study group have been examined and recommendations for biopsy made in 202 (2 per cent). Twenty-three malignancies have been confirmed so far, 12 found by mammography alone, 9 by clinical examination alone and 2 as the result of both.

In the control group, 14 breast cancers have been found in the course of normal medical care giving an incidence of 1.4 per 1,000. The study group incidence is 2.3 per 1,000.

The effect of the study on survival will require a longer follow-up.—*Henry J. Klos, M.D.*

DONEGAN, WILLIAM L., PEREZ-MESA, CARLOS M., and WATSON, FRANCIS R. A biostatistical study of locally recurrent breast carcinoma. *Surg., Gynec. & Obst.*, March, 1966, 122, 529-540. (From: Ellis Fischel State Cancer Hospital, and Cancer Research Center, Columbia, Mo.)

The experience of the Ellis Fischel State Cancer Hospital with locally recurrent breast carcinoma is reviewed by the authors. Only those patients with unilateral breast carcinoma treated for cure with radical mastectomy alone and followed for at least 5 years were considered. There were 704 such patients.

There were local recurrences in 17.5 per cent at 5 years with most occurring within 2 years of surgery and very few beyond 5 years.

Recurrences increased with quadrant tumors (as opposed to central tumors), increasing size of tumor, skin involvement (especially edema), histologically aggressive tumors, axillary lymph node involvement and reduced margin of excised skin.

Prognosis was poor with recurrence, 46 per cent dying within 1 year and 96 per cent by 5 years. Survival seemed to be increased with treatment of the local disease.

The location of lesions predominantly in the medial flap, near the site of the original tumor and

the increased recurrence rate with narrow skin margins about the removed tumor all suggest that recurrence results from transection of involved lymphatics at the time of operation.—*Henry J. Klos, M.D.*

BROWN, W. M. COURT, and DOLL, RICHARD. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Brit. M. J.*, Dec. 4, 1965, 2, 1327-1332. (Address: Mr. Brown, Director of the Medical Research Council's Clinical Effects of Radiation Research Unit, Western General Hospital, Edinburgh, Scotland.)

The authors have investigated the incidence of leukemia in man following exposure to ionizing radiation, and have also examined the nature of the relationship between the dose of radiations and the extent of the incidence of the disease. A total of 14,554 patients with ankylosing spondylitis, treated with roentgen rays during the period 1935 to 1954 was studied with more than 98 per cent follow-up.

The most important finding, apart from the previously reported excess of deaths from leukemia and aplastic anemia, relates to other cancers originating in the areas of heavily irradiated tissues. Deaths attributed to these cancers were increased approximately twofold 6 or more years after the first treatment, and 15 years after the first treatment the excess showed no sign of diminishing.

The increased incidence of other cancers was not limited to one or two types, but many different types were encountered approximately in proportion to their normal incidence. In contrast to this, the number of deaths from cancers originating in lightly irradiated tissues was not significantly increased.—*Luther W. Brady M.D.*

RADIOISOTOPES

TORRANCE, H. B., ISBISTER, W. H., and MITCHELL, G. The application of a radioactive scanning technique in diseases of the liver. *Brit. J. Surg.*, Oct., 1965, 52, 813-816. (From: Manchester Royal Infirmary, Manchester, England.)

The authors described a new method of liver scanning which they have evolved and which is different from the ordinary familiar scintiscanography.

At the outset, they selected the following criteria for an "ideal" radioactive isotope for organ scanning:

1. The isotope must emit gamma radiation of sufficient intensity to allow its distribution to be detected by external counting.
2. Uptake by the organ must be highly selective and the distribution of its material uniform.
3. The isotope must not be taken up by pathologic tissues such as carcinoma.

4. The specific radioactivity of the organ must remain constant throughout the period taken to perform the scan.

The agent which the investigators utilized was I^{131} labelled heat denatured albumin (HDA). This material is prepared from normal human serum albumin by incubation in a water bath at a fixed temperature, until a fixed increment in optical density occurs. This denaturing process results in the aggregation of the protein molecules. On intravenous injection, quite unlike normal human serum albumin, this material rapidly disappears from the circulation having been taken up by the reticuloendothelial cells in the liver and spleen. The efficiency of extraction of a single circulatory transit through the liver is approximately 90 per cent.

Following intravenous injection of I^{131} labelled HDA, liver extraction is complete within 8 minutes and the background activity from blood and other tissues is virtually zero. The liver activity remains at a constant plateau level for at least 40 minutes. This material is extracted from the sinusoidal blood within the liver by the reticuloendothelial cells and is not taken up by tumor tissue.

Approximately 75 μ c of I^{131} HDA is injected intravenously, the patient having been given a large dose of inorganic iodide over the previous 48 hours. The detector is a directional scintillation counter connected to a rate meter, which records the gamma emission from the tissue underlying the window of the counter, using suitable lead collimators. The resolution is such that it can detect a silent area about the size of a penny at a distance of 2 inches from the window of the counter, or in other words, metastases in the anterior or lateral portions of the liver in the average nonobese subject. The scanning procedure is carried out with the patient recumbent on a firm couch. A series of marks is made with a skin pencil at 1 inch intervals in the midline of the sternum and down to below the umbilicus. The counter, supported on a moving arm, is aligned along the marks in a transverse direction and the count rates recorded at 1 inch intervals, until it is obvious from the fall-off in count rate that the counter is situated outside the radioactive field of the liver. This procedure takes on an average about 30 minutes to execute.

The records from the scan are interpreted by plotting the results on graph paper, and by joining together a continuous line of points of equal activity; thereby a contour map of distribution of radioactivity within the liver is produced. It is also helpful to take a series of transverse scan lines and plot the results individually on graph paper. Using both methods of assessment, any individual scan can be quite quickly assessed for any asymmetry in distribution of radioactivity which may suggest a space-occupying lesion within the liver or deformity due to external compression. (It seems to the reviewer that the "contour

map of distribution" can be conceived as being analogous to the isodose curve constructed to measure distribution of dosage in radiation therapy, and affords a picture of the organ in an anteroposterior projection, while the plot of the individual transverse scan line affords a picture of a "slice" through a plane perpendicular to the anteroposterior projection.)

Several illustrative cases are described.

The authors state that they have investigated 46 patients during the past 5 years and have been able to compare the scan with direct examination of the liver by laparotomy, peritoneoscopy, or autopsy in the majority of cases. There were 2 false positives, and 2 false negatives. Thus the above described method of liver scanning provides a reasonably accurate prediction of the presence or absence of metastases or other space-occupying lesions within the liver, and, with refinement of the detecting apparatus and the method of recording and presenting the data obtained, this method of liver scanning will offer a further addition to the complement of preoperative investigations in patients with malignant disease arising within the abdominal cavity.—*Edwin LePar, M.D.*

HENSCHKE, U. K., and LAWRENCE, D. C.
Cesium-131 seeds for permanent implants. *Radiology*, Dec., 1965, 85, 1117-1119. (Address: Dr. Henschke, Memorial Sloan-Kettering Cancer Center, New York, N. Y.)

Low-energy gamma emitters in seed form would seem to offer several advantages over the conventional radon 222 and gold 198 seeds. The authors have made many efforts to procure low-energy seeds, and now are able to acquire cesium 131 and iodide 125 seeds, which are being produced on a limited scale by the Hazelton Nuclear Science Corporation for preliminary studies.

Cesium 131 has a half-life of 9.7 days and emits only characteristic x rays of 29.4 kev. with no beta radiation. The presently available cesium 131 seeds have a central gold filament core, to which carrier-

free cesium 131 is bound by ion exchange. This core is enclosed in a thin cold-welded aluminum jacket and an outer heat-sealed teflon capsule. The seed has dimensions of 0.8 mm. diameter and 4.5 mm. total length. These seeds withstand repeated autoclaving, can be implanted through the usual No. 17 gauge needle, and can be mass produced.

A graph accompanying this article compares cesium 131 absorption in water with that of radon 222 and gold 198 seeds, and shows the radon and gold emissions to have much greater difference in absorption in heavy metals, with the half-value layer for cesium 131 being 0.025 mm. lead, while the half-value layer for radon is 12 mm. and gold is 2.5 mm. lead. This selective absorption in heavy metals makes protection for the operator much easier to achieve, renders protection of adjacent parts easy to shield with lead foil, and makes transport and storage relatively easy in light metal containers. The absorption characteristics may also be of therapeutic benefit, and the integral body dose and exposure of distant organs less. The 9.7 day half-life appears preferable for economic reasons and possibly for therapeutic reasons.—*J. C. Moore, M.D.*

FERRI, ESTHER S., and BARATTA, EDMOND J.
Polonium 210 in tobacco, cigarette smoke, and selected human organs. *Pub. Health Rep.*, Feb., 1966, 81, 121-127. (From: Analytical Services, Northeastern Radiological Health Laboratory, Division of Radiological Health, Public Health Service, Winchester, Mass.)

Because the radioactivity of polonium 210 in tobacco might be a factor in lung cancer, the authors determined the amount of this element in the smoke of various cigarettes.

Assuming that a regular cigarette smoker uses 2 packages a day, the dose to the lungs was found to be from 33 to 95 millirems per year or 1.5 to 4.2 per cent of the maximum permissible concentration for polonium 210 in air and therefore a negligible amount.—*Henry J. Klos, M.D.*



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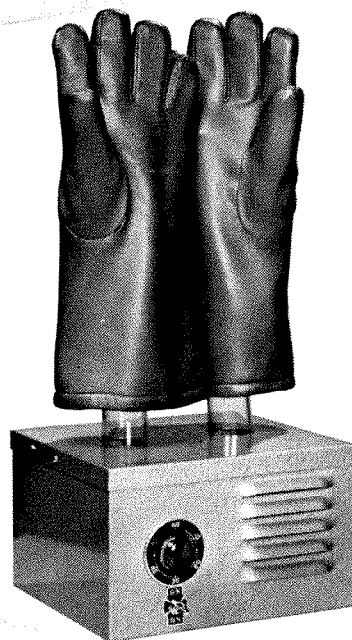
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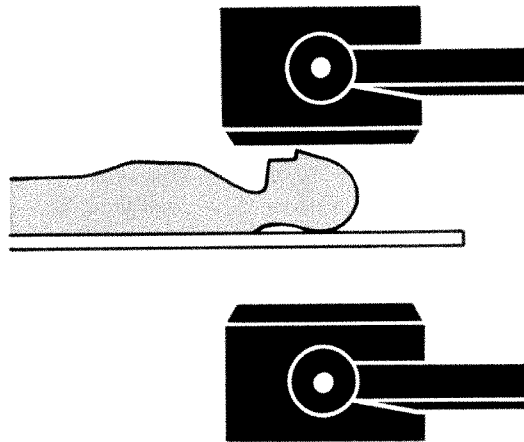
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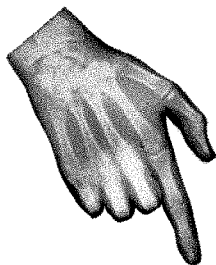
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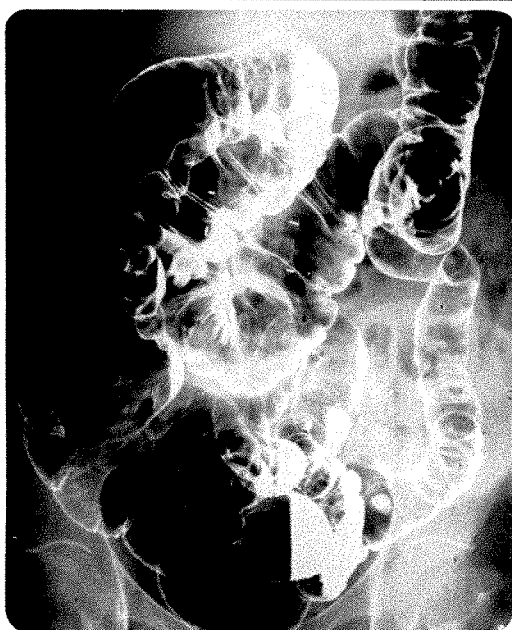
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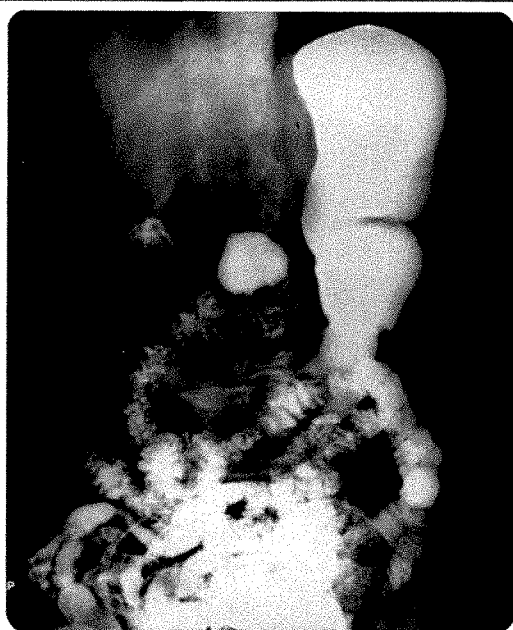
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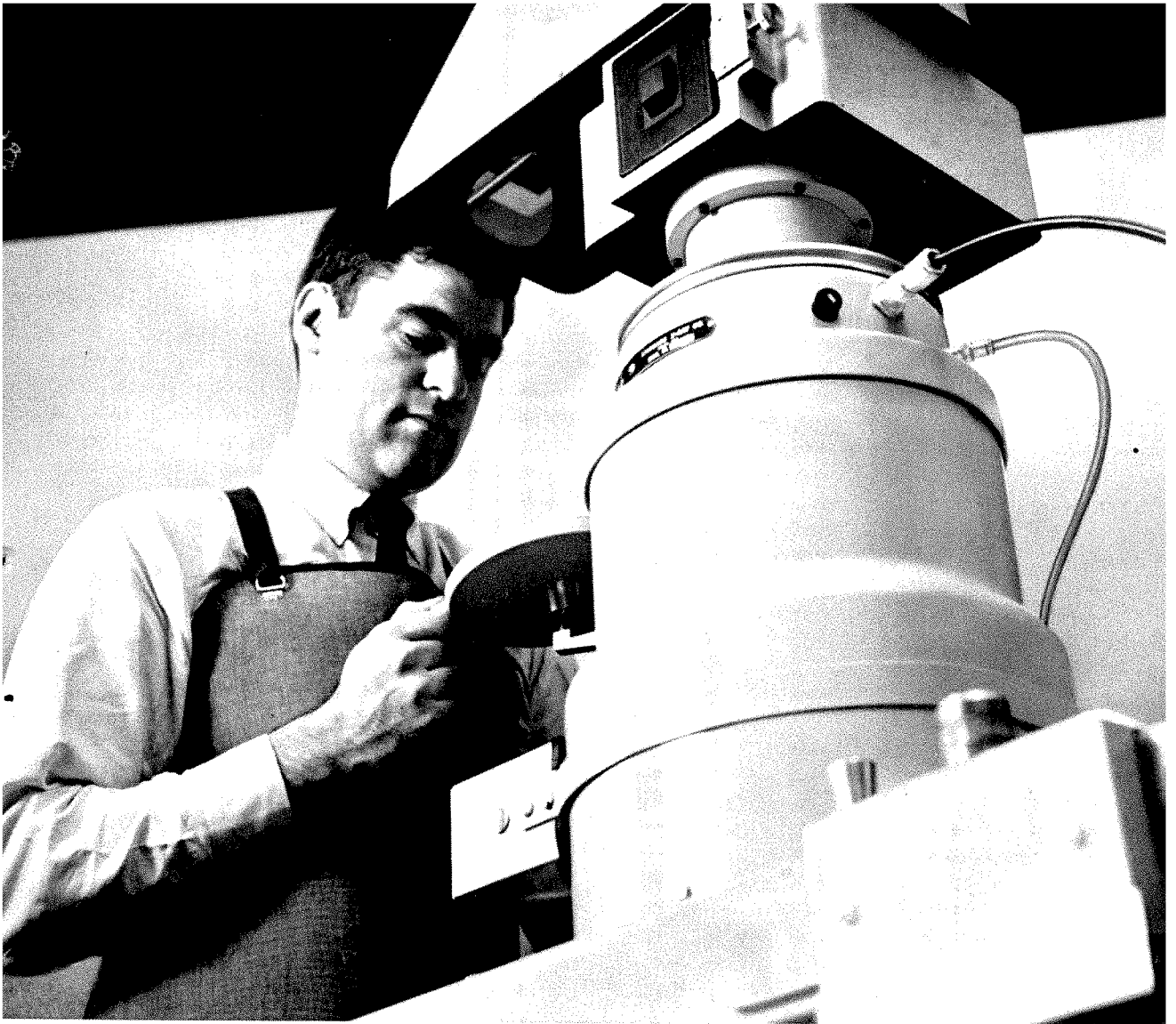


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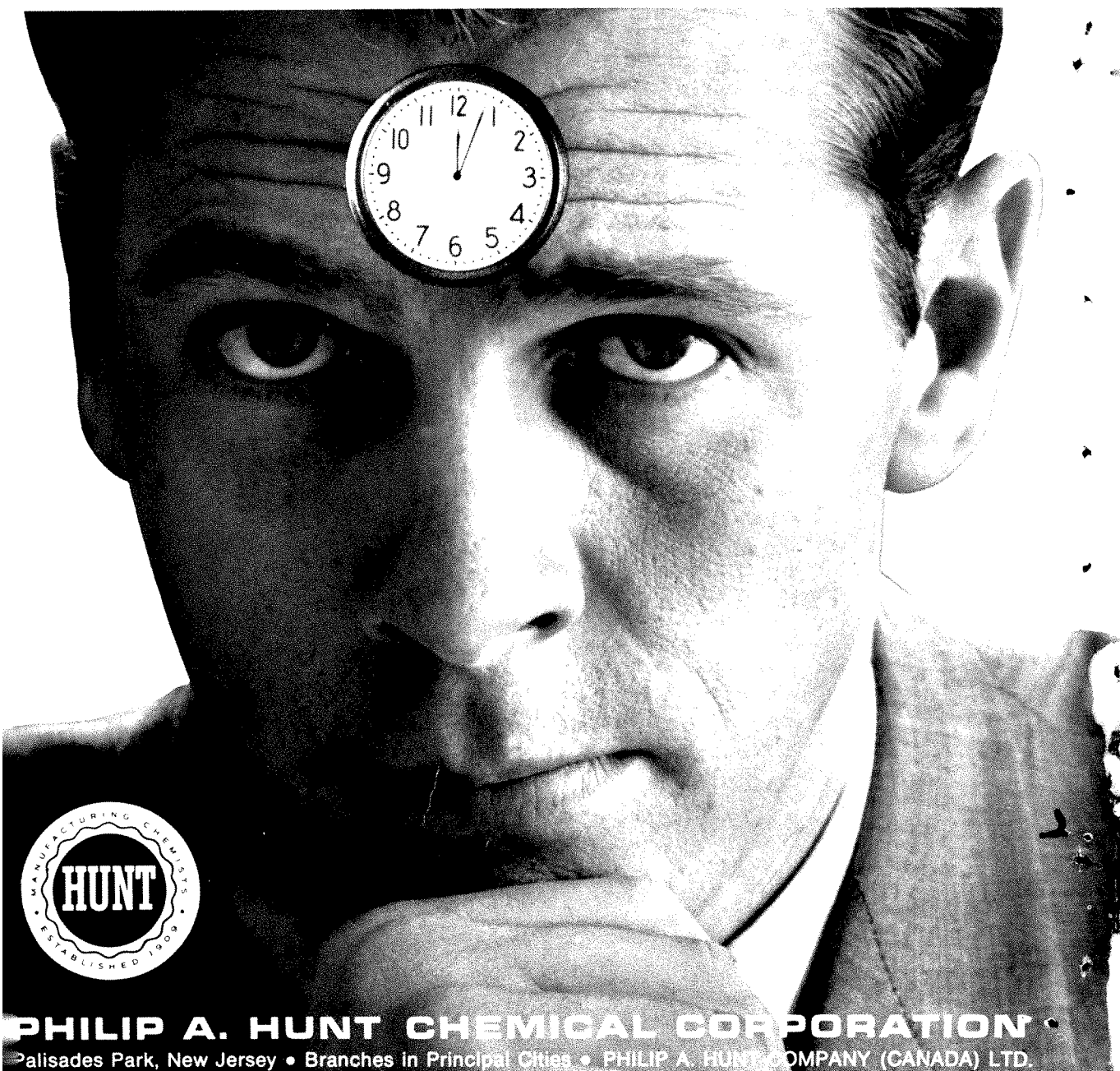
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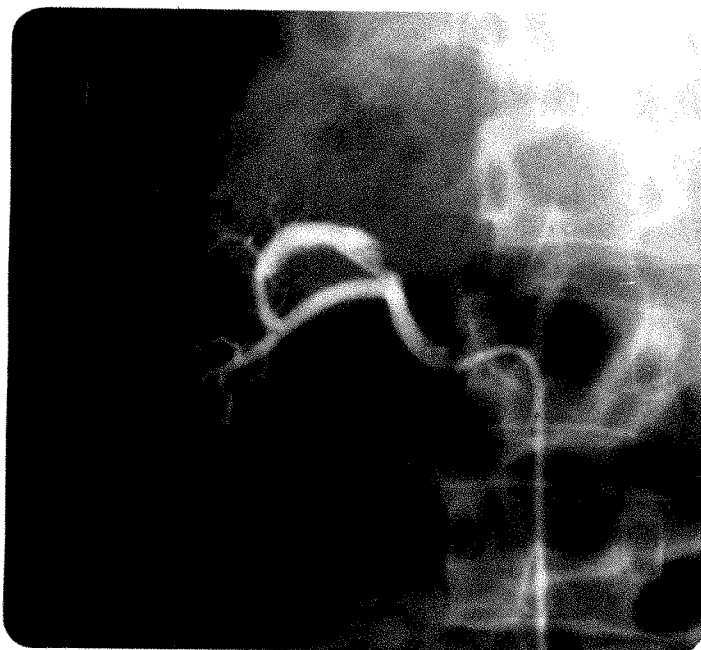
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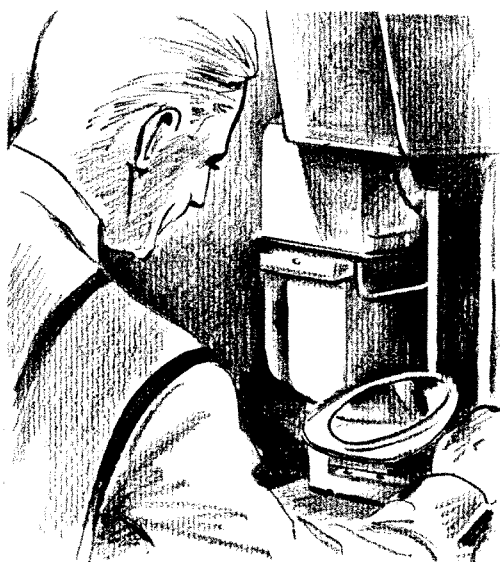
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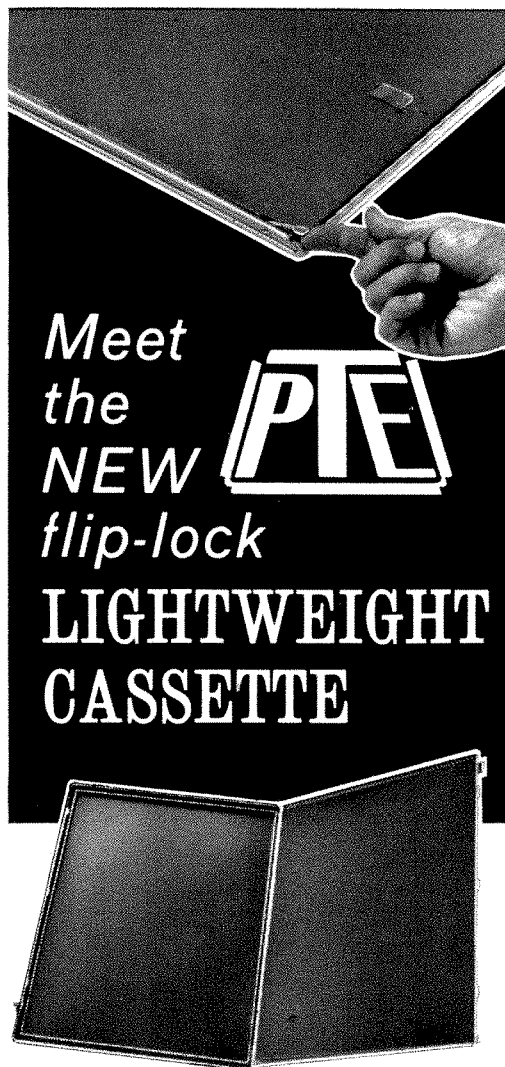


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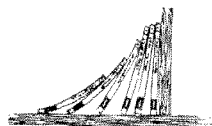
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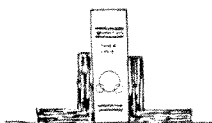
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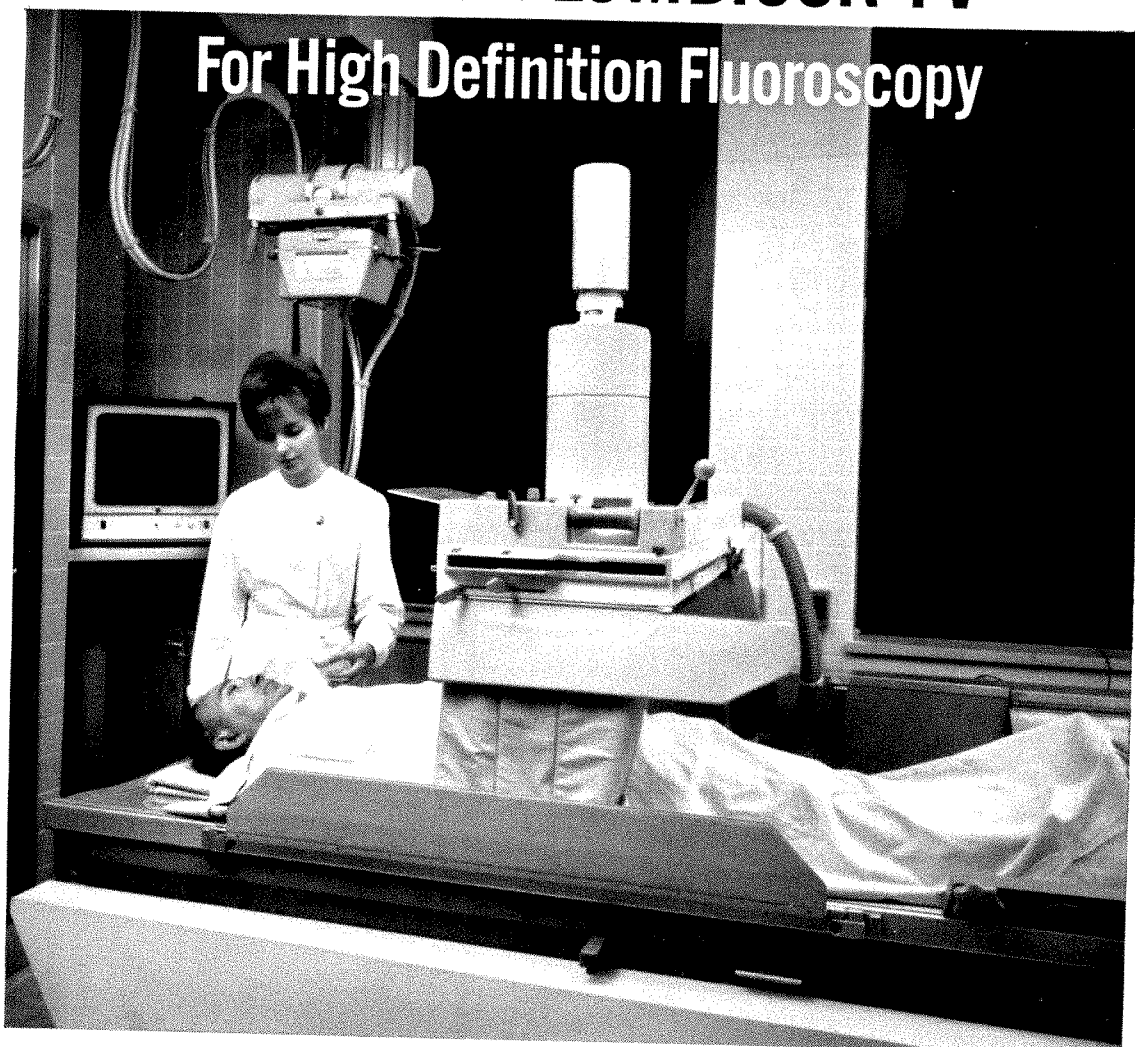


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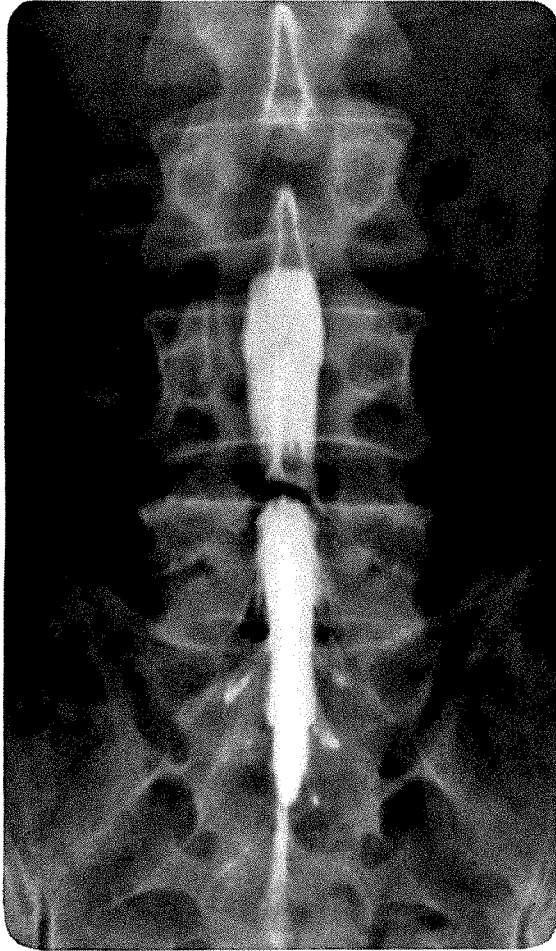
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